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(54) Title: SUBSTITUTED ARYL PYRROLES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE

(57) Abstract

The present invention addresses substituted aryl pyrroles, as well as compositions containing such compounds and methods of treatment. Cytokine mediated diseases refer to diseases or conditions in which excessive or unregulated production or activity of one or more cytokines is present. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF) are cytokines which are involved in these conditions.

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TITLE OF THE INVENTION
SUBSTITUTED ARYL PYRROLES , COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE

BACKGROUND OF THE INVENTION

The present invention addresses 2-substituted aryl pyrroles, as well as compositions containing such compounds and methods of treatment. Cytokine mediated diseases refers to diseases or conditions in which excessive or unregulated production of one or more cytokines occurs. Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Tumor Necrosis Factor (TNF) are cytokines which are involved in immunoregulation and other physiological conditions, such as inflammation. IL-1, IL-8, IL-6 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions.

There are many disease states in which IL-1 is implicated. Included among these diseases are rheumatoid arthritis, osteoarthritis, endotoxemia, toxic shock syndrome, other acute or chronic inflammatory diseases, such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, graft v. host rejection, allograft rejection, fever and myalgia due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired

immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

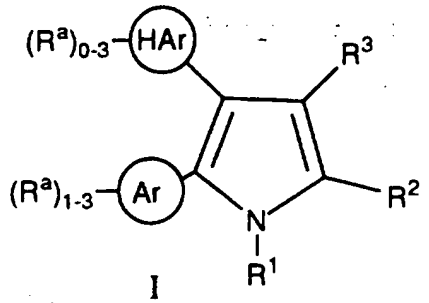
Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells. TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar reasons as those noted.

IL-6 is a cytokine effecting the immune system and hematopoiesis. It is produced by several mammalian cell types in response to agents such as IL-1 and is correlated with disease states such as angiofollicular lymphoid hyperplasia.

Interleukin-8 (IL-8) is a chemotactic factor first identified and characterized in 1987. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor. Like IL-1, IL-8 is produced by several cell types, including mononuclear cells, fibroblasts, endothelial cells and keratinocytes. Its production is induced by IL-1, TNF and by lipopolysaccharide (LPS). IL-8 stimulates a number of cellular functions in vitro. It is a chemoattractant for neutrophils, T-lymphocytes and basophils. It induces histamine release from basophils, causes lysozomal enzyme release and respiratory burst from neutrophils, and has been shown to increase the surface expression of Mac-1 (CD11b/CD 18) on neutrophils without de novo protein synthesis. There remains a need for treatment, in this field, for compounds which are cytokine suppressive, i.e., compounds which are capable of inhibiting cytokine production or activity, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

The present invention is directed to a compound represented by formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

(Ar) represents a C_{5-10} aryl group substituted with 1 - 3 groups selected from R^a ;

(HAr) represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 -3 R^a groups;

each R^a independently represents a member selected from the group consisting of: halo; CN, NO_2, R^{21}; OR^{23}; SR^{23}; $S(O)R^{21}$; SO_2R^{21}; $NR^{20}R^{23}$; $NR^{20}COR^{21}$; $NR^{20}CO_2R^{21}$; $NR^{20}CONR^{20}R^{23}$; $NR^{20}SO_2R^{21}$; $NR^{20}C(NR^{20})NHR^{23}$, CO_2R^{23}; $CONR^{20}R^{23}$; $SO_2NR^{20}R^{23}$; $SO_2NR^{20}COR^{21}$; $SO_2NR^{20}CONR^{20}R^{23}$; $SO_2NR^{20}CO_2R^{21}$; $OCONR^{20}R^{23}$; $OCONR^{20}SO_2R^{20}$; $C(NR^{20})NR^{20}R^{23}$; $CONR^{20}SO_2R^{21}$; $SO_2NR^{20}CO_2R^{21}$ and tetrazol-5-yl;

R^1 is selected from the group consisting of: H; C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, aryl and heterocyclyl, said alkyl, alkenyl, aryl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, CO_2R^{23}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $C(O)OCH_2OC(O)R^{20}$ and $OCONR^{20}R^{23}$;

R^2 is selected from the group consisting of: heterocyclyl; C_{1-15} alkyl, C_{2-15} alkenyl, and C_{2-15} alkynyl, said alkyl, alkenyl and alkynyl groups being optionally interrupted by 1-2 oxo groups or heteroatoms selected from O, S, S(O), SO_2 or NR^{24}; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from 1-3 of halo, aryl, aryl$(R^a)_3$, heteroaryl, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $C(O)R^{22}$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}C(O)NR^{20}R^{21}$, $NR^{20}C(O)NHR^{21}$, $NR^{20}C(O)R^{21}$, $N(R^{22})C(NR^{22})NHR^{22}$, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$ and $OCONR^{20}R^{23}$;

R^3 is selected from the group consisting of: CN, $S(O)R^{21}$, SO_2R^{21}, COR^{20}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CON(R^{20})_2$, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and $SO_2NR^{20}CO_2R^{21}$;

R^{20} represents a member selected from the group consisting of: H, C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

R^{21} represents a member selected from the group consisting of: C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, optionally interrupted by

1-2 heteroatoms selected from O, S, S(O), SO_2 or NR^{24}; heterocyclyl, aryl and heteroaryl;

said alkyl, alkenyl, alkynyl, heterocyclyl, aryl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, CN, OR^{20}, $O((CH_2)_nO)_mR^{20}$, $NR^{20}((CH_2)_nO)_mR^{20}$ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{22}C(NR^{22})NHR^{22}$, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OCONHR^{20}R^{23}$ and $OCON(R^{20})_2$;

R^{22} is selected from the group consisting of: C_{1-15} alkyl, C_{2-15} alkenyl, C_{2-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

R^{23} is R^{21} or H;

R^{24} is selected from aryl, COR^{22}, CO_2R^{22}, $CON(R^{20})_2$, R^{23} and SO_2R^{22};

and in a functional group substituent, when two R^{20} groups are present, when R^{20} and R^{21} are present, or when R^{20} and R^{23} are present, said two R^{20} groups, R^{20} and R^{21} or said R^{20} and R^{23} may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said hetercyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

Also included in the invention is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

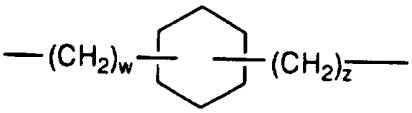
Also include in the invention is a method of treating a cytokine mediated disease in a mammal, comprising administering to a mammalian patient in need of such treatment an amount of a compound of formula I which is effective to treat said cytokine mediated disease.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred straight or branched alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and t-butyl. Preferred cycloalkyl groups include cyclopentyl and cyclohexyl.

Alkyl also includes a straight or branched alkyl group which contains or is interrupted by a cycloalkylene portion or a carbonyl group. Examples of cycloalkylene interruption include the following:

and


wherein: x and y = from 0-10; and w and z = from 0-9. Examples of carbonyl interruption include $-(CH_2)_x-C(O)-(CH_2)_y-$.

The alkylene and monovalent alkyl portion(s) of the alkyl group can be attached at any available point of attachment to the cycloalkylene portion.

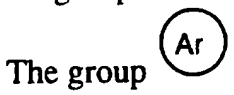
When substituted alkyl is present, this refers to a straight, branched or cyclic alkyl group as defined above, substituted with 1-3 groups as defined with respect to each variable.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 15 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic (non-resonating) carbon-carbon double bonds may be present. Preferred

alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted when a substituted alkenyl group is provided.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 15 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Preferred alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted when a substituted alkynyl group is provided.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and like groups as well as rings which are fused, e.g., naphthyl and the like. Aryl thus contains at least one ring having at least 6 atoms, with up to two such rings being present, containing up to 10 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms. The preferred aryl groups are phenyl and naphthyl. Aryl groups may likewise be substituted as defined below. Preferred substituted aryls include phenyl and naphthyl substituted with one or two groups.

The group  represents a 5-10 membered aryl group substituted with 1 - 3 groups selected from R^a. Preferred Ar are phenyl and naphthyl.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one additional carbon atom is optionally replaced by a heteroatom selected from O or S, and in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms. The heteroaryl group is optionally substituted with up to three groups.

Heteroaryl thus includes aromatic and partially aromatic groups which contain one or more heteroatoms. Examples of this type are thiophene, purine, imidazopyridine, pyridine, oxazole, thiazole, oxazine, pyrazole, tetrazole, imidazole, pyridine, pyrimidine and pyrazine and triazine.

The group  represents a heteroaryl group which contains from 5 to 10 atoms. One to three atoms are heteroatoms which are selected from O, S and N. In addition, there may be up to two additional nitrogen atoms, and 0-1 additional O or S. The heteroaryl group may be unsubstituted or substituted with 1 -3 R^a groups. HAr is carbon linked except where it is a purinyl, imidazolyl or imidazopyridine in which case it may be attached at the nitrogen or carbon atom.

Preferred heteroaryl groups represented by  are as follows: pyridyl, quinolyl, purinyl, imidazolyl, imidazopyridyl and pyrimidinyl.

The terms "heterocycloalkyl" and "heterocyclyl" refer to a cycloalkyl group (nonaromatic) in which one of the carbon atoms in the ring is replaced by a heteroatom selected from O, S or N, and in which up to three additional carbon atoms may be replaced by said heteroatoms.

The heterocyclyl is carbon or nitrogen linked, if said heterocyclyl is carbon linked and contains a nitrogen, then nitrogen may be substituted with the variable group R^{24}. The group may be interrupted by or contain one or two carbonyls. Examples of heterocyclyls are piperidinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydroimidazo[4,5-c]pyridine, imidazolinyl, piperazinyl, pyrrolidine-2-one, piperidine-2-one and the like.

The term "TNF mediated disease or disease state" refer to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is

exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

The term "cytokine" as used herein is meant any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α) and Tumor Necrosis Factor-beta (TNF-β).

The terms "cytokine interfering" and "cytokine suppresive amount" mean an effective amount of a compound of formula I which decreases in the *in vivo* levels or activity of the cytokine to normal or sub-normal levels, when given to the patient for the prophylaxis or therapeutic treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production or activity.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All such compounds are included in the present invention.

One subset of compounds of the invention relates to compounds of formula I wherein Ar represents a substituted phenyl group. Within this subset, all other variables are as originally defined.

Another subset of compounds of the invention relates to compounds of formula I wherein R^a is selected from the group consisting of: halo; CN, R^{21}; OR^{23}; CO_2R^{23}; $CONR^{20}R^{23}$ and tetrazol-5-yl. Within this subset, all other variables are as originally defined.

Another subset of compounds of the invention relates to compounds of formula I wherein HAr represents a substituted or unsubstituted pyridyl, quinolyl, purinyl, imidazolyl or imidazopyridyl group. Within this subset, all other variables are as originally defined.

Another subset of compounds of the invention relates to compounds of formula I wherein R^1 is H, $C_{1\text{-}15}$ alkyl or $C_{1\text{-}15}$ alkyl substituted as originally defined. Within this subset, all other variables are as originally defined.

Another subset of compounds of the invention relates to compounds of formula I wherein R^2 represents one of the following groups:

a) C_{1-7} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$,

b) C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$,

c) C_{1-4} alkyl-aminoacyl-C_{2-6} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$,

d) C_{1-4} alkyl-aminoacyl-C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo, $N(R^{20})_2$ or NR^{24},

e) C_{1-4} alkyl-aminoacylamino-C_{2-6} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$, or

and f) C_{1-4} alkyl-aminoacylamino-C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo,$N(R^{20})_2$ or NR^{24}. Within this subset, all other variables are as originally defined.

Another subset of compounds of the invention relates to compounds of formula I wherein R^3 represents CO_2R^{20} , $CONR^{20}R^{23}$ or CN. Within this subset, all other variables are as originally defined.

A preferred subset of compounds of formula I is thus realized when:

Ar is phenyl;

R^a represents a member selected from the group consisting of: halo; CN, R^{21}; OR^{23}; CO_2R^{23}; $CONR^{20}R^{23}$ and tetrazol-5-yl;

HAr is an optionally substituted:

a) pyridyl,
b) quinolyl,
c) purinyl,
d) imidazolyl, or
e) imidazopyridine;

R^1 is:

a) H or
b) substituted or unsubstituted C_{1-15} alkyl;

R^2 is:

a) C_{1-7} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by : oxo or $N(R^{20})_2$,

b) C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by : oxo or $N(R^{20})_2$,

c) C_{1-4} alkyl-aminoacyl-C_{2-6} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by : oxo or $N(R^{20})_2$,

d) C_{1-4} alkyl-aminoacyl-C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by : oxo, $N(R^{20})_2$ or NR^{24},

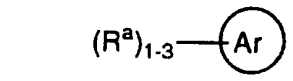
e) C_{1-4} alkyl-aminoacylamino-C_{2-6} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by : oxo or $N(R^{20})_2$, or

f) C_{1-4} alkyl-aminoacylamino-C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by: oxo,$N(R^{20})_2$ or NR^{24};

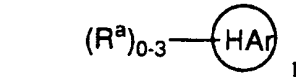
R^3 is: a) CO_2R^{20};

b) $CONR^{20}R^{23}$ or
c) CN.

A subset of the most preferred compounds of formula I is realized when:


represents a member selected from the group consisting of:

a) 4-fluorophenyl,
b) 4-chlorophenyl,
c) 3-fluorophenyl,
d) 3-chlorophenyl,
e) 3-methylphenyl,
f) 3,4-dichlorophenyl, and
g) 3-hydroxyphenyl;


represents a member selected from the group consisting of:

a) 4-pyridyl,
b) 4-(2-methylpyridyl),
c) 4-(2-aminopyridyl),
d) 4-(2-methoxypyridyl),
e) 4-quinolyl,
f) 4-pyrimidinyl,
g) 9-purinyl,
h) 7-(imidazo[4,5-b]pyridinyl), and
i) 4-(3-methylpyridyl);

R^1 is H;

R^2 is selected from the group consisting of:

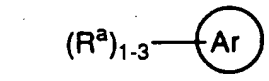
a) isopropyl,
b) tert-butyl,
c) phenethyl,

d) benzyl,
e) 2-amino-2,2-dimethylethyl,
f) 4-aminomethylbenzyl,
g) glycylaminomethyl,
h) (L)-alanylaminomethyl,
i) 2-amino-2,2-dimethylacetylaminomethyl,
j) N,N-dimethylaminoethyl-N-methylaminocarbonylaminomethyl,
k) 3-piperidinecarbonylaminomethyl,
l) 4-piperidinecarbonylaminomethyl,
m) piperidine-4-yl,
n) piperidine-3-yl,
o) pyrrolidin-3-yl,
p) N-methylpiperidine-4-yl,
q) N-benzylpiperidine-4-yl, or
r) N-(2-hydroxyeth-1-yl)piperidine-4-yl;
s) N-methanesulfonylpiperidine-4-yl, and

R^3 is selected from the group consisting of:

a) CO_2R^{20};
b) $CONR^{20}R^{23}$ and
c) CN.

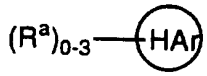
Another subset of the most preferred compounds is realized when:



represents a member selected from the group consisting of:

a) 4-fluorophenyl,
b) 4-chlorophenyl,
c) 3-fluorophenyl,
d) 3-chlorophenyl,
e) 3-methylphenyl,
f) 3,4-dichlorophenyl, and

g) 3-hydroxyphenyl;


represents a member selected from the group consisting of:

a) 4-pyridyl,
b) 4-(2-methylpyridyl),
c) 4-(2-aminopyridyl),
d) 4-(2-methoxypyridyl),
e) 4-quinolyl,
f) 4-pyrimidinyl,
g) 9-purinyl,
h) 7-(imidazo[4,5-b]pyridinyl), and
i) 4-(3-methylpyridyl);

R^1 is C_{1-15} alkyl;

R^2 is selected from the group consisting of:

a) isopropyl,
b) tert-butyl,
c) phenethyl,
d) benzyl,
e) 2-amino-2,2-dimethylethyl,
f) 4-aminomethylbenzyl,
g) glycylaminomethyl,
h) (L)-alanylaminomethyl,
i) 2-amino-2,2-dimethylacetylaminomethyl,
j) N,N-dimethylaminoethyl-N-methylaminocarbonylaminomethyl,
k) 3-piperidinecarbonylaminomethyl,
l) 4-piperidinecarbonylaminomethyl,
m) piperidine-4-yl,
n) piperidine-3-yl,
o) pyrrolidin-3-yl,

p) N-methylpiperidine-4-yl,
q) N-benzylpiperidine-4-yl, or
r) N-(2-hydroxyeth-1-yl)piperidine-4-yl;
s) N-methanesulfonylpiperidine-4-yl and

R^3 is selected from the group consisting of:
a) CO_2R^{20};
b) $CONR^{20}R^{23}$ and
c) CN.

The pharmaceutically acceptable salts of the compounds of formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of formula I formed e.g. from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention.

This invention also relates to a method of inhibiting the production or activity of cytokines in a mammal in need thereof which

comprises administering to said mammal an effective amount of a compound of formula I to inhibit cytokine production or activity, such that it is regulated down to treat, ameliorate or prevent the disease state.

The compounds of formula 1 can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of disease states in mammals, which are exacerbated or caused by excessive or unregulated cytokine production, more specifically IL-1, IL-8 or TNF production, by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of formula I inhibit proinflammatory cytokines, such as IL-1, IL-8 and TNF and are therefore useful for treating inflammation diseases such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions.

The compounds of formula I may be used to treat other disease states mediated by excessive or unregulated TNF production. Such diseases include, but are not limited to sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis. bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host rejection, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDs related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, AIDS and other viral infections, such as cytomegalia virus (CMV), influenza virus, and the herpes family of viruses such as Herpes Zoster or Simplex I and II.

The compounds of formula I may also be used topically in the treatment of inflammations such as for the treatment of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Interleukin-1 (IL-1) has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions. [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

The compounds of formula I are also useful in treating diseases characterized by excessive IL-8 activity. There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases include psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis.

The invention includes a method of treating psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis, in a mammal in need of such treatment which comprises administering to said mammal a compound of formula I in an amount which is effective for treating said disease or condition.

The compounds of formula I are normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. This invention, therefore, also relates to a pharmaceutical

composition comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. The compounds of formula I are administered in conventional dosage forms prepared by combining a compound of formula I with standard pharmaceutical carriers according to conventional procedures. The compounds of formula I may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known in the art, such as glyceryl mono-stearate or glyceryl distearate, alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be in the form of a tablet, hard gelatin capsule, a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 0.025 mg to about 1 g. When a liquid carrier is used, the preparation is in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The compounds of formula I may be administered topically. Thus the compounds of formula I may be administered topically in the form of a liquid, solid or semi-solid. Liquids include solutions, suspensions and emulsions. Solids include powders, poultices and the like. Semi-solids include creams, ointments, gels and the like.

The amount of a compound of formula I, for all methods of use disclosed herein, required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the condition, whether and the discretion of

the physician. A representative, topical, antiinflammatory dose of a compound of formula I is from about 0.01 mg to about 2.0 g, administered one to four, preferably one to two times daily.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from about 0.001% to about 90% w/w.

Drops according to the present invention may comprise sterile aqueous or oil solutions or suspensions, and may be prepared by dissolving the active ingredient in a suitable aqueous solution, optionally including a bactericidal and/or fungicidal agent and/or any other suitable preservative, and optionally including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0:01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous liquid, with the aid of suitable machinery, with a

greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or macrogels. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicas, and other ingredients such as lanolin may also be included.

The methods of the instant invention may be carried out by administering the compound of formula I to a patient in need of such treatment. The term 'parenteral' as used herein includes intravenous, intramuscular, or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. The instant invention can also be carried out by delivering the monokine activity interfering agent subcutaneous intranasally, intrarectally, transdermally, or intravaginally

The compounds of formula I may also be administered by inhalation. By 'inhalation' is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by convention techniques.

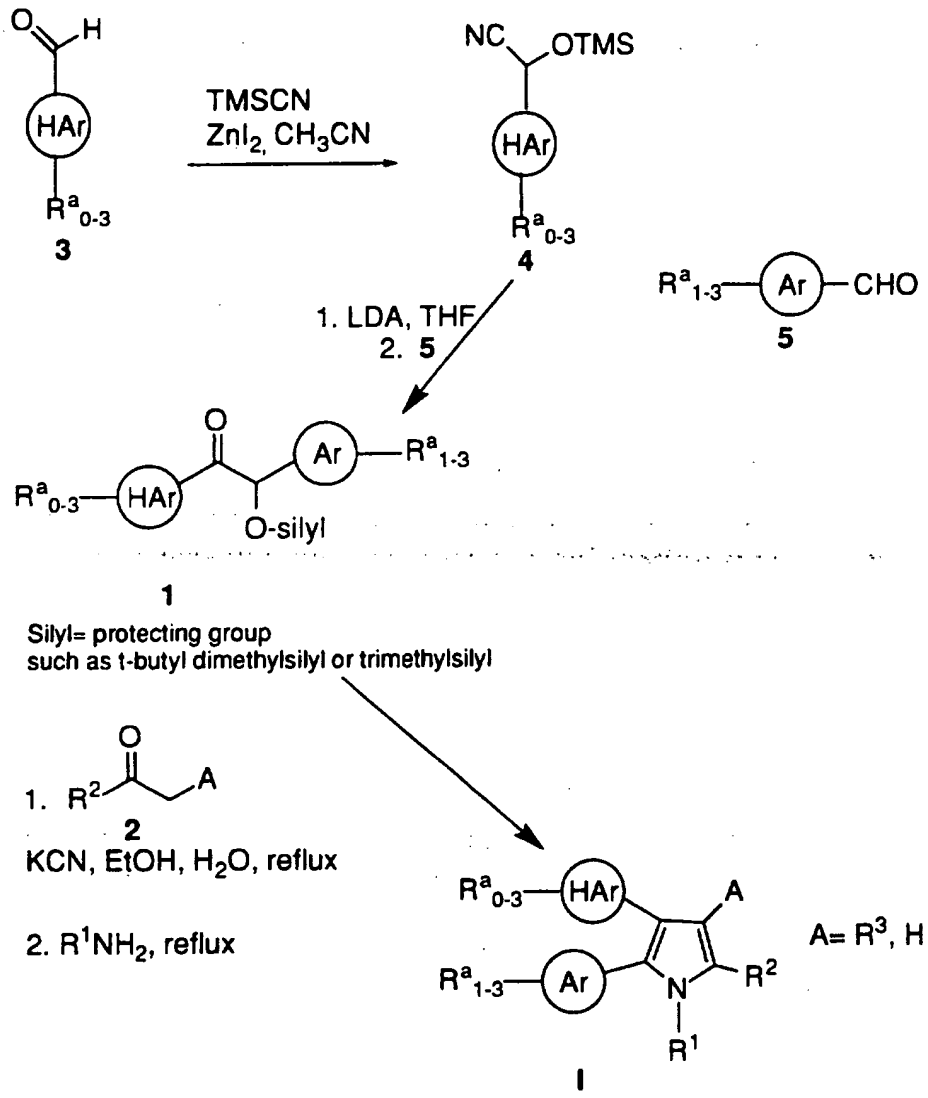
Compounds of formula I are pyrrole derivatives which may be prepared by one skilled in the art according to the procedures setforth below. The key process in preparing compounds of formula I is the formation of a pyrrole ring with specific substituents on the heterocycle.

Compounds of formula I are prepared (see Scheme I) by the reaction of compound **1**, or protected version thereof with an aceto-phenone in the presence of potassium cyanide followed by treatment with an alkyl or aryl amine, ammonia or equivalent thereof (ammonium acetate) at elevated temperature.

Compound **1** is prepared as described below. Hetero-

aromatic aldehydes **3** are converted to their trimethylsilyl cyanohydrins **4**. Deprotonation and reaction with an aldehyde **5** provides trimethyl silyl protected benzoins **1** (Hunig, S.; Wehner, G. Chem. Ber. *112*, 2062 1979).

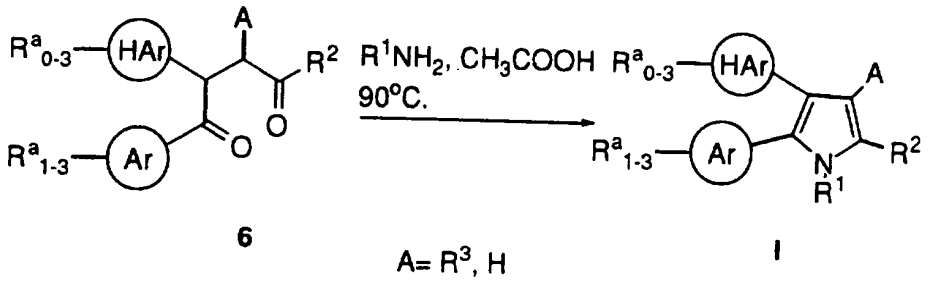
SCHEME I



The condensation of a 1,4-diketone with ammonia gives rise to pyrroles (Paal Knor Synthesis). A 1,4 diketone such as **6** is reacted with ammonia (or a compound that gives rise to ammonia such

as ammonium acetate) or a primary amine to provide compounds of formula 1 generally in the presence of an acid catalyst such as acetic acid or titanium tetrachloride (See Scheme II). 1,4 diketones **6** are thus regioselectively constructed so that the appropriate groups are present on the pyrrole ring.

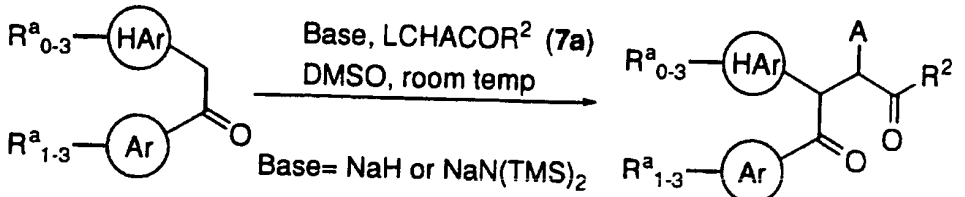
SCHEME II



6 **I**

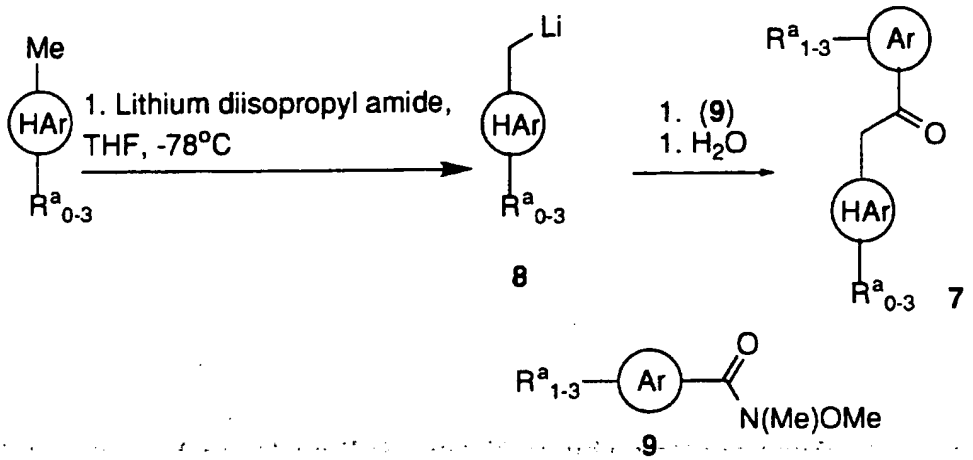
A= R^3, H

Alkylation of 1-aryl-2-heteroarylethanones **7** with an alpha-leaving group substituted ketone **7a** provides 1,4 diketones **6** (Iyer, R. N.; Gopalachari, R. Ind. J. Chem. *11*, 1260, (1973)). The alkylating agent **7a** is prepared by various methods such as: free radical or acid catalyzed bromination of a ketone; halogenation of a ketone enolate; conversion of the hydroxyl group of an alpha-hydroxy ketone to a leaving group such as the bromide, triflate, tosylate or mesylate; reaction of an acid chloride with diazomethane followed by reaction with hydrogen chloride gives an alpha-chloro ketone.

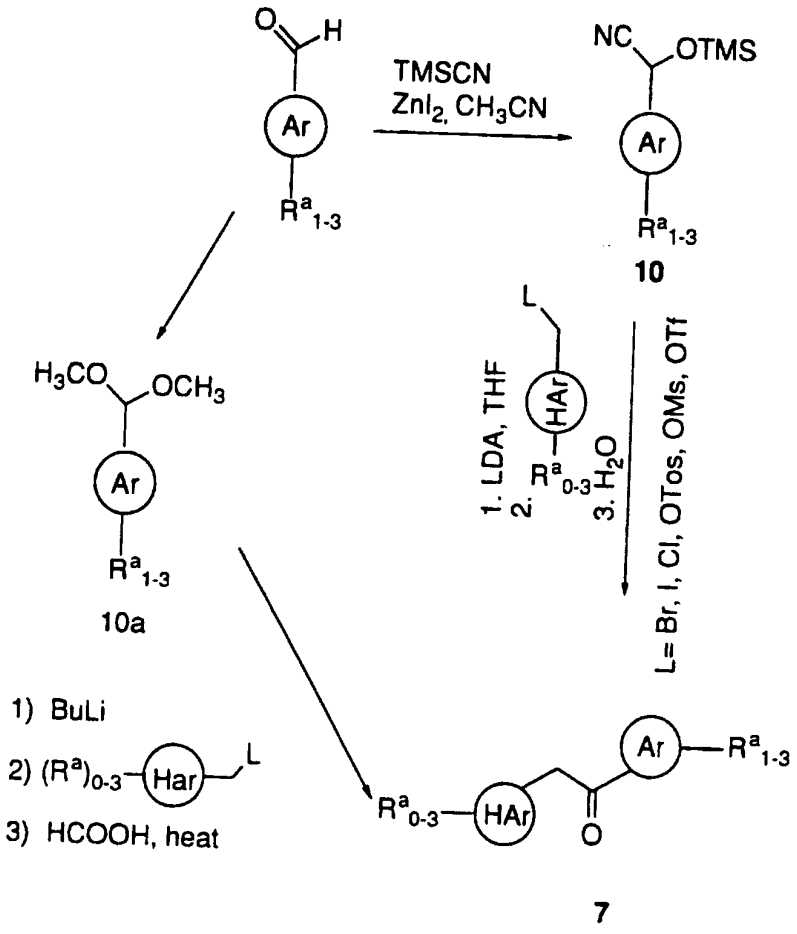


7 **6**

Ethanones **7** are prepared by addition of heteroaryl methyl anions **8** to activated benzoic acids **9** (for example esters, acid chlorides, nitriles and N-methoxy-N-methyl amides) (see: Wolfe, J. F. et al J. Org. Chem. *39*, 2006 (1974) and Kaiser, E. M. et al. Synthesis 705 (1975) and Ohsawa A. Chem. Pharm. Bull. *26*, 3633, (1978)).



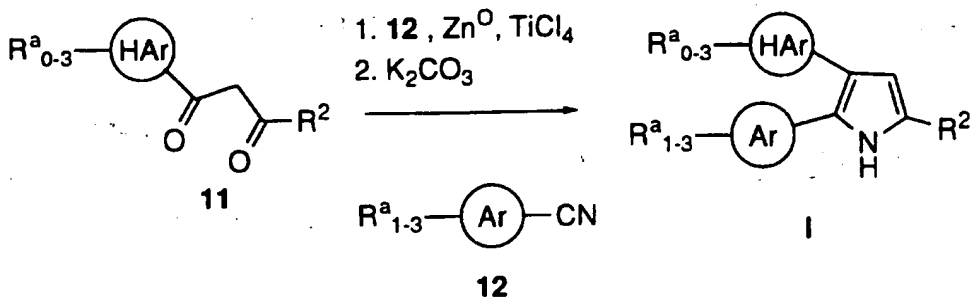
An alternative approach to **7** is via alkylation of aryl trimethyl silyl protected cyanohydrins **10**. Treatment of **10** with lithium diisopropyl amide in THF and addition of a heteroaryl methyl group functionalized with a leaving group L (for example:Br, I, Cl , tosylate, mesylate) followed by acid catalyzed hydrolysis of the silyl cyanohydrin group provides ethanones such as **7** (Deuchert, K.; Hertenstein, U.; Hunig, S.; Wehner, G. Chem. Ber. *112*, 2045, (1979)).



Dimethylacetal **10a** may be prepared from aldehydes by reaction with trimethylorthoformate and an acid catalyst. Addition of a base such as butyl lithium followed by an alkylating agent after hydrolysis of the acetal, also provides **7**.

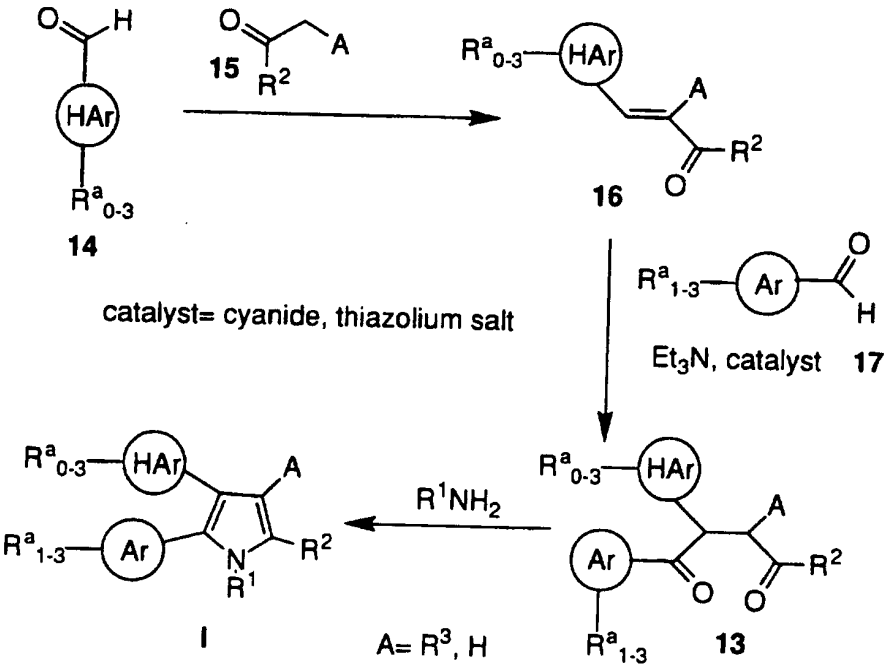
The reductive cross coupling of 1,3 diketones **11** with a nitrile **12** in the presence of zinc and titanium tetrachloride give rise to compounds of formula I (Gao, J. Hu, M.; Chen, J.; Yuan, S.; Chen, W. Tet Lett. *34*, 1617, (1993)). 1,3 diketones **11** is prepared by alkylation of **4** with bromoacetophenones (See Scheme III).

SCHEME III



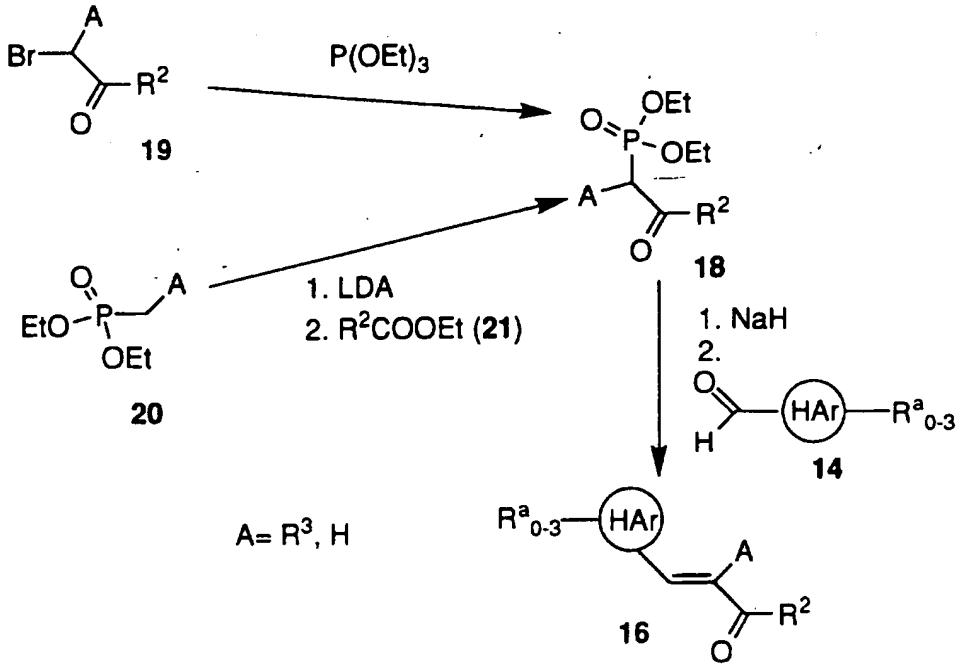
1,4 diketones **13** are also prepared as described above in Scheme IV. A heteroaryl aldehyde **14** is condensed with a methyl ketone **15** to provide α, β-unsaturated ketone **16**. In the presence of a catalyst such as cyanide or a thiazolium salt, an aryl aldehyde **17** reacts with **16** to give **13** (Stetter, H. J. et al Heterocyclic Chem. **14**, 573, 1977 and Stetter, H. et. al. Organic Reactions, Vol 40, 407-496). Condensation of **13** with an amine provides compounds of formula I.

SCHEME IV



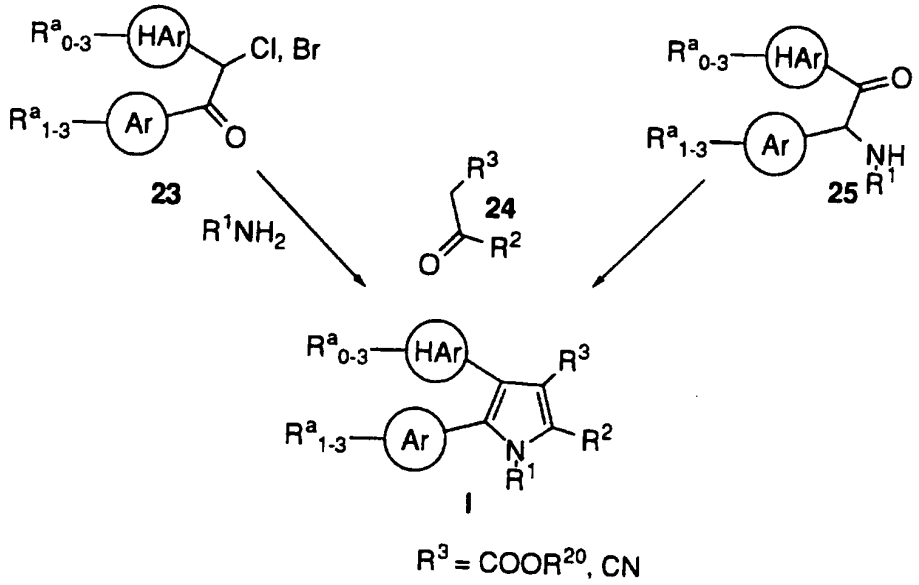
Intermediate **16** may be prepared by a Horner-Emmons reaction of the anion of **18** with the heteroaryl aldehyde **14**. The reagent **18** is prepared by reaction of the bromoketone **19** and triethyl phosphite or by reaction of the lithium salt of diethyl methylphosphonate with an ester **21**.

SCHEME V



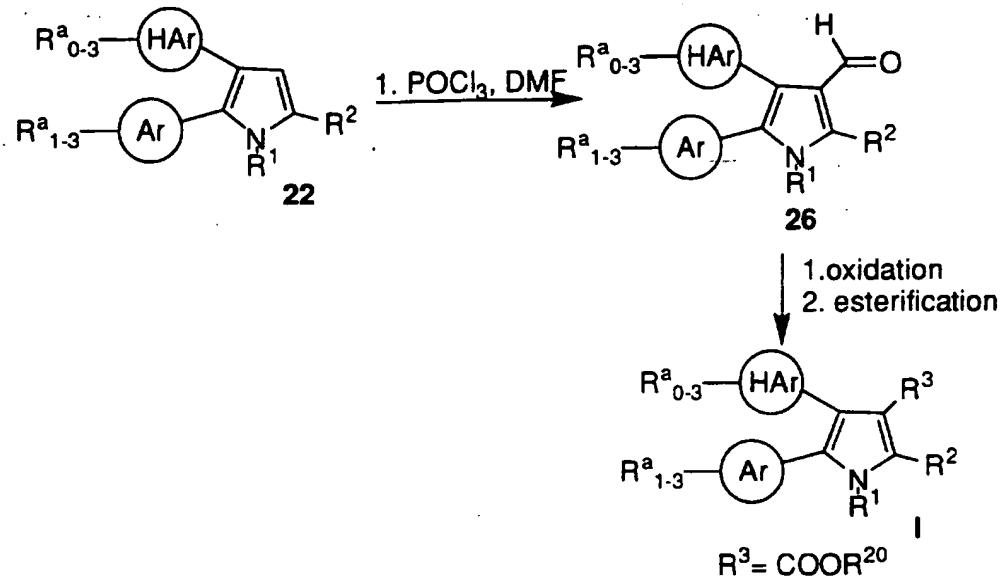
The ester and nitrile of formula I may be prepared as shown in Scheme VI by treatment of 1,2 disubstituted-2 halo ketones **23** with **24** with ammonia or an amine producing ester **I** (Hantzsch. Ber. Dtsch. Chem. Ges. **23**, 1474, **1890**). Alternatively a 2-amino ketone **25** reacts with **24** to produce **I**.

SCHEME VI



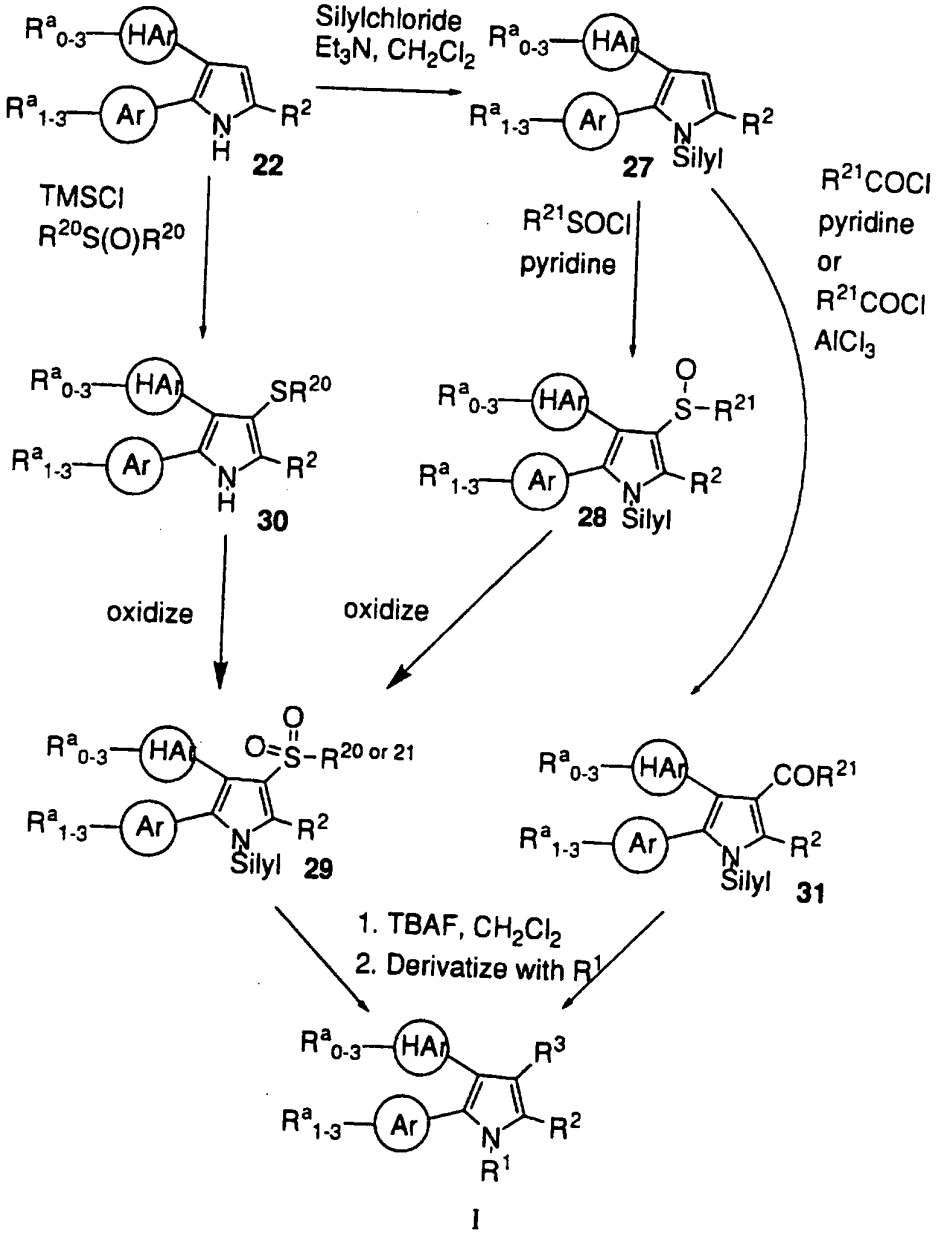
A further method of synthesis of Compounds of formula I is by oxidation and esterification of aldehyde **26**. The aldehyde is prepared by treatment of the R^3 -unsubstituted pyrrole **22** with the Villsmeyer reagent ($POCl_3$/DMF).

SCHEME VII



The pyrrole **22** may be silylated on nitrogen to give **27** by treatment with a silyl chloride and base in a solvent such as methylene chloride. The pyrrole **27** may then be sulphinylated with a sulphinyl-chloride under basic conditions to provide **28** (J. Org Chem 6317, **1990**). Oxidation of **28** with a reagent such as m-chloroperoxybenzoic acid or potassium persulfate will give the sulphone **29**. Removal of the silyl group and derivatization of the pyrrole will give compounds of Formula I. **22** may also be converted to the sulphide **30** by reaction of **22** with a symmetrical sulfoxide in the presence of trimethylsilylchloride to give **30**. Oxidation of **30** with a reagent such as m-chloroperoxybenzoic acid will give **29**. The silyl pyrrole **27** may also be acylated with an acid chloride to give the ketone **31**. Removal of the silyl group from **31** and derivatization of the pyrrole will give compounds of Formula I. Pyrroles such as **22** may also be sulphinylated directly without N-protection, by treatment with sulphinyl chlorides in a solvent such as dichloromethane at 0°C (J. Org. Chem. 5336, **1980**). Oxidation as described above may provide pyrroles of Formula I where R^3 is SO_2R^{21}

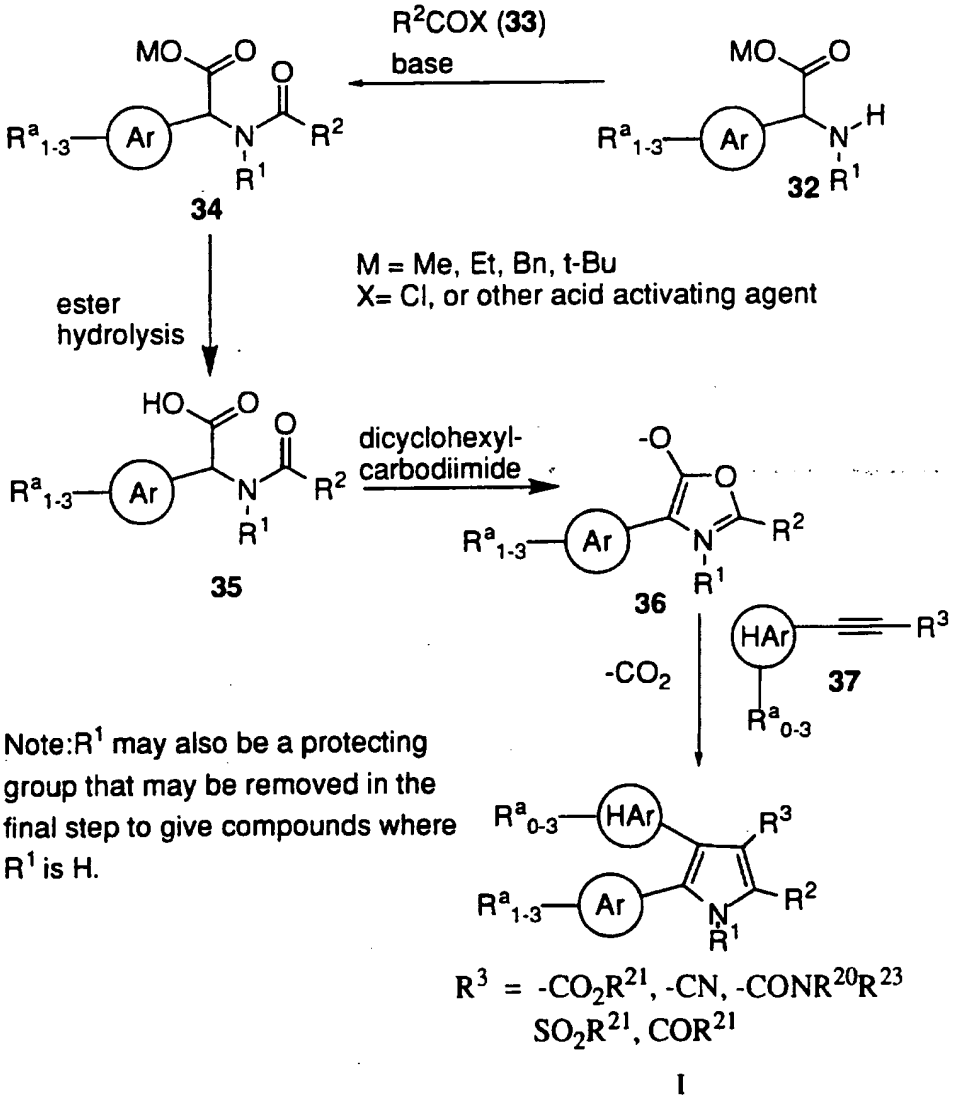
SCHEME VIII



The amino acid ester **32** may be acylated with an acid **33** that is suitably activated (acid chloride or other activating group used in amide coupling reactions) to give **34**. Hydrolysis of the ester protecting

group will privide **35**. Cyclization by treament with an acid activating group such as DCC will give the oxazolium species **36**. Addition of an alkyne **37** to **36** may give a pyrrole of Formula I via a 3+2 cycloaddition followed by loss of carbon dioxide. Various R^3 groups may be incorporated in this manner.

Scheme IX

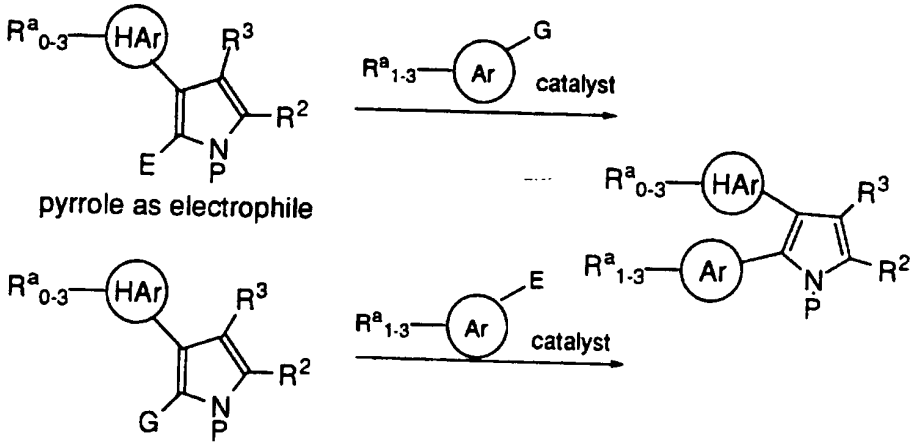


Note:R^1 may also be a protecting group that may be removed in the final step to give compounds where R^1 is H.

R^3 = $-CO_2R^{21}$, -CN, $-CONR^{20}R^{23}$
SO_2R^{21}, COR^{21}

I

SCHEME X



E=: Br, I, OSO_2CF_3
G=: $SnMe_3$, $B(OH)_2$, ZnCl, MgBr
catalyst=: $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$
P=R^1 or protecting group such as trialkyl silyl, benzyl, substituted benzyl, t-butyloxycarbonyl

Aryl and heteroaryl rings are appended to the pyrrole ring system by utilization of organometallic coupling technology (Kalinin, V. Synthesis 413 **1991**). Two alternative approaches are utilized for appending aryl and heteroaryl rings to the pyrrole ring. The pyrrole ring functions as the electrophile or as the nucleophile.

Any of the two appended aromatic or heteroaromatic rings is attached to the pyrrole ring system (Alvarez, A. J. et al. J. Org. Chem. 1653, (1992) (use of boronic acid and tributyl stannanes for coupling to aromatic and heteroaromatic rings)). Attachment of pyrrole pendant groups is carried out with or without other Ar, HAr, R^2 or R^3 groups attached. R^2 groups are introduced through the use of the Heck reaction (Heck, R. F. Org. React. (1982), *27*, 345) in which alkenes are coupled with heteroaryl halides. Alkynes are coupled with heteroaryl halides to give alkyne substituents at R^2. These R^2=alkene and alkyne groups may, in turn be reduced to alkanes by hydrogenation.

The synthesis of pyrroles containing nucleopilic groups for coupling reactions depends on the pyrrole substitution pattern. Lithium anions are prepared by metalation of a regioselectively halogenated pyrrole, or the regioselective deprotonation of the pyrrole preferably by the use of a directing functional group. The resulting anion may then be trapped by a trialkyl stannyl halide or a trialkyl borate or transmetalated to magnesium or zinc by treatment with appropriate halide salts. A further method used to incorporate a trialkyl stannyl group is the coupling of a bromo, iodo or triflate substituted pyrrole with hexalkylditin in the presence of a palladium catalyst.

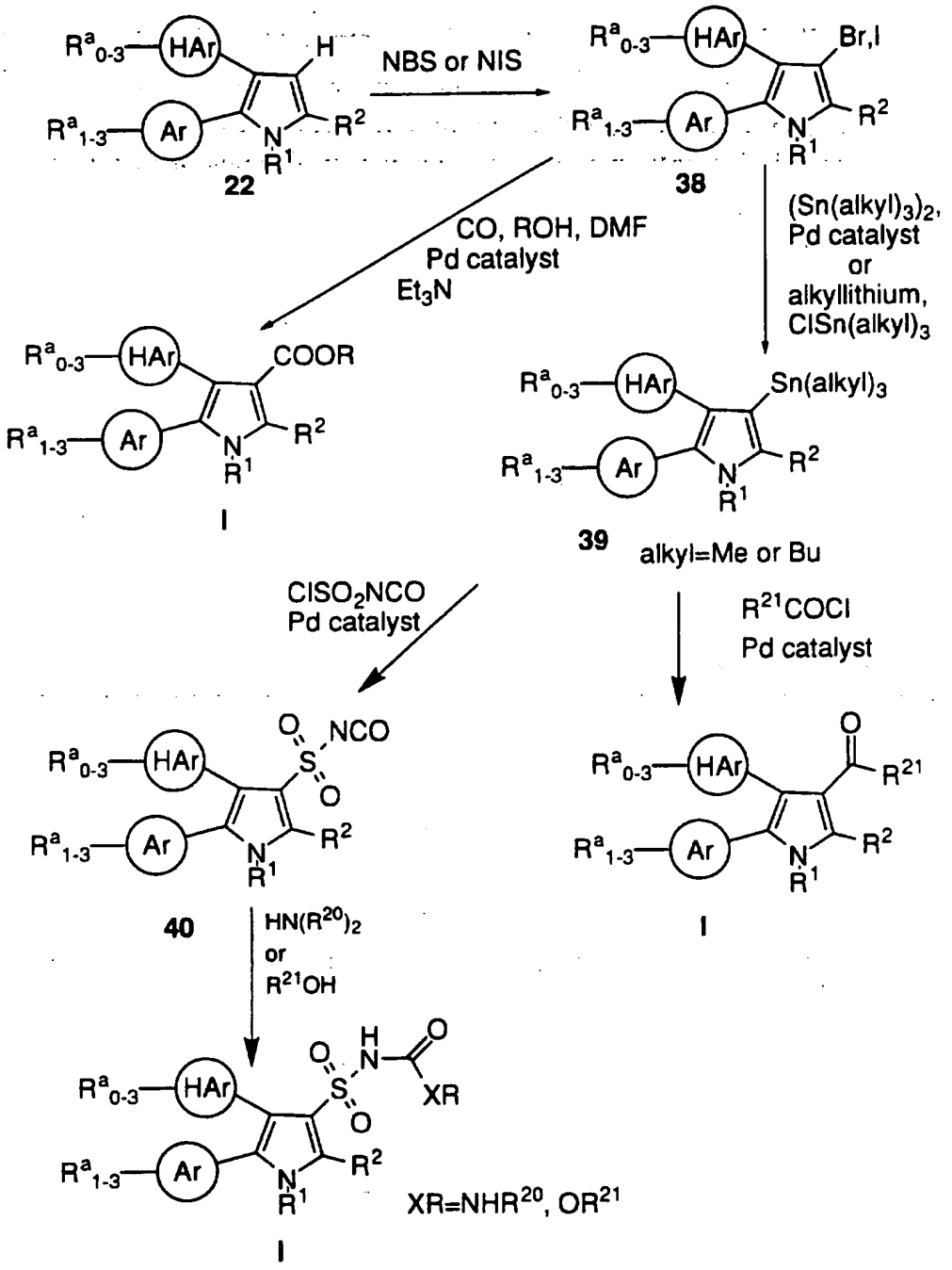
The synthesis of pyrroles incorporating electrophilic groups may be carried out by the regioselective halogentation of a pyrrole (Pyrroles Part 1, R. Alan Jones,ed., Heterocyclic Compounds ,Vol 48 Part 1, John Wiley, New York, 349-391,(1990)). The regioselectivity of halogenation will depend on the size, nature and substitution position on the pyrrole ring as well as the presence or absence of the N-alkyl protecting group. Triflates may be prepared by acylation of hydroxy pyrroles with triflic anhydride.

The reaction conditions used will depend on the nature of the coupling species. In the case of magnesium, zinc and stannyl coupling reactions the solvent used is normally toluene or DMF under anhydrous conditions. In the case of boronic acid couplings a heterogenous system is used of water, toluene, dimethoxyethane or ethanol in the presence of a base such as sodium carbonate or bicarbonate. In general the reaction takes place at an elavated temperature (80-100 °C). Catalysts used depend on the structure of the components to be coupled as well as the functional groups. Most commonly, tetrakistriphenylphosphinepalladium (0) or palladium bis triphenyl phosphine dichloride are utilized.

Coupling chemistry may be utilized to introduce R^3 groups as shown below in Scheme X. 4-unsubstituted pyrroles **22** may be halogenated by treatment with electrophilic sources of bromine and iodine to provide **38**. The halogen may then be coupled with carbon monoxide in the presence of an alcohol after the removal of any

protecting groups to give 4-alkoxycarbonyl substituted pyrroles of formula I. Treatment of **38** with a hexalkylditin in the presence of a palladium catalyst (see above for examples of catalysts) will give the stannyl pyrrole **39**. Alternatively, halogen metal exchange through treatment of **38** with an alkyl lithium followed by addition of a trialkyltinchloride will give **39**. The stannyl pyrrole may then be coupled to acid chlorides to give ketones of formula I. Reaction of **39** with chlorosulfonylisocyanate in the presence of a palladium catalyst will give the sulphonyl isocyanate **40**. **40** may subsequently be converted to a sulphonyl urea or sulphonyl carbamate of fomula I by addition of a primary or secondary amine or an alcohol.

Scheme XI


NBS or NIS
22
38
CO, ROH, DMF
Pd catalyst
Et3N
(Sn(alkyl)3)2,
Pd catalyst
or
alkyllithium,
ClSn(alkyl)3
I
39
alkyl=Me or Bu
ClSO2NCO
Pd catalyst
R21COCl
Pd catalyst
40
HN(R20)2
or
R21OH
I
XR=NHR20, OR21
I

Functional groups such as halogens, sulfides, nitro groups, ethers and other groups stable to the reaction conditions used in the linear synthesis of the pyrroles are incorporated in the initial steps of the reaction sequence. Sulfides may be oxidized to sulfoxides and sulfones with reagents such as m-chloroperbenzoic acid. Sulfides may also be converted to sulfonyl chlorides by oxidation and chlorination by chlorine in water.

Sulphonyl chlorides may be converted to sulphonamides through the addition of ammonia or amines of Formula I. Sulphonamides may be acylated with phosgene or carbonyl diimidazoles and then aminated with an amine to give sulphonyl ureas or treated with an alcohol to provide sulphonyl carbamates of Formula I. Acylation of a sulphonamide with an activated carboxylic acid will give an acyl suphonamide of Formula I.

Carboxylic acids may be activated by conversion to an acid chloride or reaction with a peptide coupling reagent such as carbonyl diimidazole or dicyclohexylcarbodiimide and then reacted with amines to give amides or sulphonamides to provide acylsulphonamides.

Primary amines are prepared from nitro groups by catalytic (Pd/C, H_2 or Raney Nickel, H_2) or chemical means ($CoCl_2$, $NaBH_4$). Alkylation of amines to give secondary and tertiary amines is achieved by reductive alkylation (aldehyde, $NaCNBH_4$) or alkylation with an alkyl group substituted with a leaving group in the presence of a base such as K_2CO_3. Tertiary amines may, alternatively, be carried through the reaction sequences to the pyrroles. Acylation of primary or secondary amines with activated acids, chloroformates, isocyanates and chlorosufonates will give rise to amides, carbamates, ureas and sulonamides, respectively.

Other methods of preparing amides and ureas are useful: such as for example, treatment of the amine with phosgene, or an equivalent thereof, followed by acyaltion of an alcohol or amine with the intermediate activated chloroformamide.

Carboxylic acids are best introduced as esters early in the synthesis. Saponification will provide carboxylic acids.

Transesterification or esterification of the acids will give esters. Carboxylic acids may be converted to amides by activation and reaction with amines. Phenols are best introduced in a protected form early in the synthetic sequence to the pyrrole. Removal of the protecting group provides a phenol which may subsequently be alkylated in the presence of an alkylating agent and base to give an ether, or acylated with an isocyanate to give carbamates. Phenols may be converted to aryl ethers by reaction with an aryl bismuthane in the presence of copper II acetate.

Aryl and heteroaryl groups may be attached to pyrrole pendant aryl and heteroaryl groups by application of coupling chemistry technology as outlined above. Aryl and heteroaryl rings are appended to the pyrrole ring system by utilization of organometallic coupling technology (Kalinin, V. Synthesis 413 **1991**). Two alternative approaches are utilized for appending aryl and heteroaryl rings to the pyrrole ring. The pyrrole ring functions as the electrophile or as the nucleophile.

Any of the two appended aromatic or heteroaromatic rings is attached to the pyrrole ring system. (Alvarez, A. J. et al J. Org. Chem. 1653, (1992) (use of boronic acid and tributyl stannanes for coupling to aromatic and heteroaromatic rings)). Attachment of pyrrole pendant groups is carried out with or without other Ar, HAr, R^2 or R^3 groups attached. R^2 groups are introduced through the use of the Heck reaction (Heck, R. F.Org. React. (1982), *27*, 345) in which alkenes are coupled with heteroaryl halides. Alkynes are coupled with heteroaryl halides to give alkyne substituents at R^2. These R^2=alkene and alkyne groups may, in turn be reduced to alkanes by hydrogenation.

The synthesis of pyrroles containing nucleopilic groups for coupling reactions depends on the pyrrole substitution pattern. Lithium anions are prepared by metalation of a regioselectively halogenated pyrrole, or the regioselective deprotonation of the pyrrole preferably by the use of a directing functional group. The resulting anion may then be trapped by a trialkyl stannyl halide or a trialkyl borate or transmetalated to magnesium or zinc by treatment with appropriate halide salts. A further method used to incorporate a trialkyl stannyl group is the coupling

of a bromo, iodo or triflate substituted pyrrole with hexalkylditin in the presence of a palladium catalyst.

The synthesis of pyrroles incorporating electrophilic groups may be carried out by the regioselective halogentation of a pyrrole (Pyrroles Part 1, R. Alan Jones,ed., Heterocyclic Compounds ,Vol 48 Part 1, John Wiley, New York, 349-391,(1990)). The regioselectivity of halogenation will depend on the size, nature and substitution position on the pyrrole ring as well as the presence or absence of the N-alkyl protecting group. Triflates may be prepared by acylation of hydroxy pyrroles with triflic anhydride.

The reaction conditions used will depend on the nature of the coupling species. In the case of magnesium, zinc and stannyl coupling reactions the solvent used is normally toluene or DMF under anhydrous conditions. In the case of boronic acid couplings a heterogenous system is used of water, toluene, dimethoxyethane or ethanol in the presence of a base such as sodium carbonate or bicarbonate. In general the reaction takes place at an elavated temperature (80-100 °C). Catalysts used depend on the structure of the components to be coupled as well as the functional groups. Most commonly, tetrakistriphenylphosphinepalladium (0) or palladium bis triphenyl phosphine dichloride are utilized.

The preparation of 4-halo substituted pyrroles may be accomplished by treatment of 2,3,5, trisubstituted pyrroles with halogens. Alkyl substituents at the 4 position of the pyrrole may be introduced through the synthesis of the 1,2,3,4-tetrasubstituted 1,4-diketone followed by cyclization with ammonia or an amine. Alternatively, coupling of alkenes or alkynes with 4-halo pyrroles (Heck reaction, see Kalinin, V. Synthesis 413 (1991) for a review) will give rise to alkenyl and alkynyl substituted pyrroles that may be reduced or otherwise modified to provide compounds of formula I.

Functional groups such as halogens, sulfides, nitro groups, ethers and other groups stable to the reaction conditions used in the linear synthesis of the pyrroles are incorporated in the initial steps of the reaction sequence. Sulfides may be oxidized to sulfoxides and sulfones with reagents such as m-chloroperbenzoic acid. Sulfides may also be

converted to sulfonyl chlorides by oxidation and chlorination by chlorine in water.

Primary amines are prepared from nitro groups by catalytic (Pd/C, H_2 or Raney Nickel, H_2) or chemical means ($CoCl_2$, $NaBH_4$). Alkylation of amines to give secondary and tertiary amines is achieved by reductive alkylation (aldehyde, $NaCNBH_4$) or alkylation with an alkyl group substituted with a leaving group in the presence of a base such as K_2CO_3. Tertiary amines may, alternatively, be carried through the reaction sequences to the pyrroles. Acylation of primary or secondary amines with activated acids, chloroformates, isocyanates and chlorosufonates will give rise to amides, carbamates, ureas and sulonamides, respectively.

Other methods of preparing amides and ureas are useful: such as for example, treatment of the amine with phosgene, or an equivalent thereof, followed by acyaltion of an alcohol or amine with the intermediate activated chloroformamide.

Carboxylic acids are best introduced as esters early in the synthesis. Saponification will provide carboxylic acids. Transesterification or esterification of the acids will give esters. Carboxylic acids may be converted to amides by activation and reaction with amines. Phenols are best introduced in a protected form early in the synthetic sequence to the pyrrole. Removal of the protecting group provides a phenol which may subsequently be alkylated in the presence of an alkylating agent and base to give an ether, or acylated with an isocyanate to give carbamates. Phenols may be converted to aryl ethers by reaction with an aryl bismuthane in the presence of copper II acetate.

Aryl and heteroaryl groups may be attached to pyrrole pendant aryl and heteroaryl groups by application of coupling chemistry technology as outlined above.

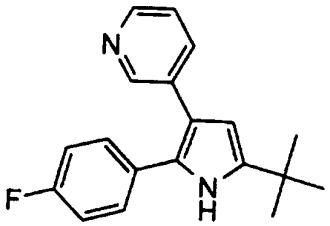
All of the above secondary conversions are well known to one skilled in the art. The sequence and conditions of the reaction steps is dependant on the structure and functional groups present. Protecting groups may be necessary and may be chosen with reference to Greene, T.W., et al., Protective Groups in Organic Synthesis, John Wiley & Sons,

Inc., 1991. The blocking groups are readily removable, i.e., they can be removed, if desired, by procedures which will not cause cleavage or other disruption of the remaining portions of the molecule. Such procedures include chemical and enzymatic hydrolysis, treatment with chemical reducing or oxidizing agents under mild conditions, treatment with fluoride ion, treatment with a transition metal catalyst and a nucleophile, and catalytic hydrogenation.

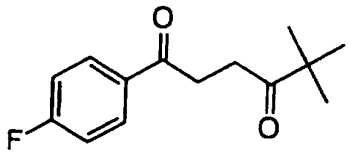
Examples of suitable hydroxyl protecting groups are: t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, trimethylsilyl, triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, and allyloxycarbonyl. Examples of suitable carboxyl protecting groups are benzhydryl, o-nitrobenzyl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyldimethoyl-silyl, t-butldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxy-benzyl, acetonyl, p-methoxyphenyl, 4-pyridylmethyl and t-butyl.

The following examples are illustrative and are not limiting of the compounds of this invention.

PREPARATIVE EXAMPLE 1



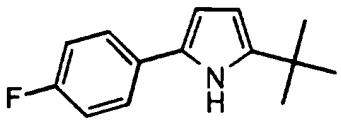
Step 1



A solution of pinacolone (0.01 m) in 10 ml of THF -78°C is treated with a solution of sodium hexamethyl disilazide (0.011 m) in THF. After

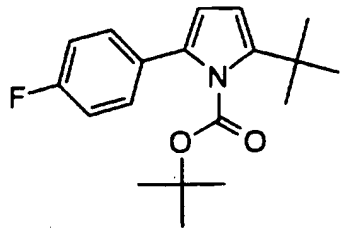
stirring for 10 minutes a solution of 4-fluorobromoacetophenone (0.011 m) in THF is added. The reaction mixture is allowed to warm to room temperature over 2 hours. 20 ml of water is added and the reaction mixture is extracted with ethyl acetate (3 x 10 ml). The combined organic phases are washed with brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo. The product is purified by flash chromatography over silica gel.

Step 2



The product of Step 1 is dissolved in acetic acid and treated with 10 times its weight of ammonium acetate. The mixture is heated at 110°C for 2 hours, cooled to room temperature and diluted with water and ethyl acetate. The aqueous phase is extracted with ethyl acetate. The combined organic phases are washed with brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo to provide the product. The product is purified further by recrystalization or chromatography over silica gel.

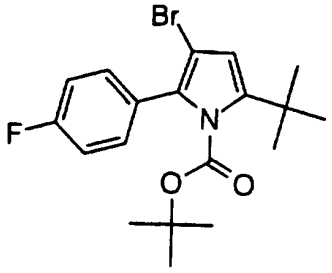
Step 3



The product of step 2 is dissolved in THF and treated with 1.1 equivalents of t-butoxycarbonyl anhydride, 0.1 equivalents of triethyl amine and 0.1 equivalents of dimethylaminopyridine. The solution is stirred at room temperature over night, diluted with ethyl acetate and

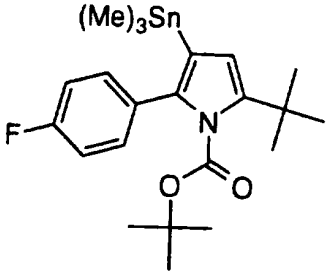
washed with water. The organic phases are washed with brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo to provide the product. The product is purified by flash chromatography over silica gel.

Step 4



A solution of the product of Step 3 in THF at -75°C is treated with 1.1 eqivalents of N-bromosuccinimide portionwise over 1 hour. The reaction mixture is allowed to warm to 0°C over 2 hours and then stirred over night. The reaction mixture is concentrated in vacuo and then triturated with carbon tetrachloride. The solid succinimide is removed by filtration and the filtrate is concentrated in vacuo to give the desired product.

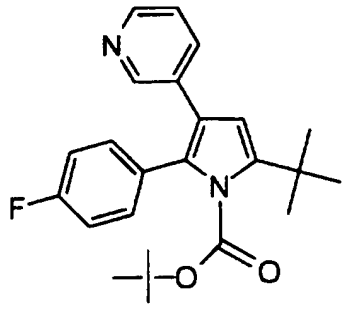
Step 5



A solution of the product of Step 4 in DMF is treated with 1.5 equivalents of 3-trimethylstannyl pyridine and 0.1 equivalents of bis-triphenylphosphine palladium dichloride. The reaction mixture is heated

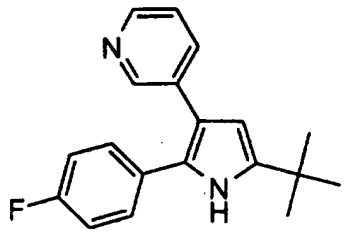
to 90°C for 3 hours, cooled and diluted with ethyl acetate and is washed with water. The organic phase are washed with brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo to provide the product. The product is purified by flash chromatography over silica gel.

Step 6



A solution of the product of Step 5 in DMF is treated with 3-chloropyridine and 0.1 equivalent of bis(triphenylphosphine) palladium dichloride. The reaction mixture is heated at 100°C until the starting material is consumed. The mixture is diluted with ethyl acetate and washed with water and brine, and is then dried over $MgSO_4$. The mixture is filtered and the residue is concentrated in vacuo. The residue is purified by flash chromatography over silica gel.

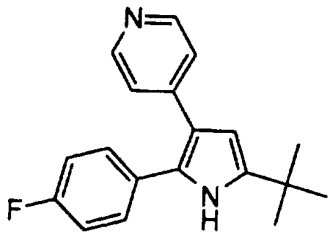
Step 7



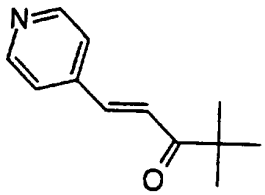
To a 0.3 M solution of the product of Step 6 in anhydrous THF under nitrogen was added 3 equivalents of sodium methoxide in methanol solution. After 3 hours at room temperature the reaction

mixture was diluted with ethyl ether and water. The aqueous phase was extracted with ether and the combined ethereal extracts were washed with brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo to provide the product. The product is purified by flash chromatography over silica gel.

PREPARATIVE EXAMPLE 2



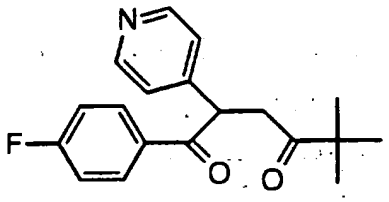
Step 1



To a solution of 10 g (0.25 m) of sodium hydroxide in 150 ml of ethanol was added a mixture of 5 g (0.05 m) pinacolone and 5.35 g (0.05 m) of 4-pyridaldehyde in 10 ml of ethanol. After 3 hours the reaction mixture was diluted with 300 mL of EtOAc and 100 ml of water. The phases were seperated and the organic phase was washed with water (2 x 100 ml) and brine (100 ml) and dried over $MgSO_4$. The mixture was filtered and the filtrate was dried in vacuo. The product was purifed by crystalization from ethanol and water.

H^1-NMR ($CDCl_3$, 300 MHz): 1.22 (s, 9H); 7.26 (d, 1H); 7.41 (m, 2H); 7.56 (d, 1H); 8.74 (m, 1H).

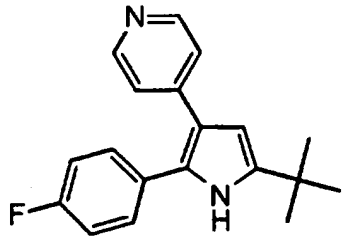
Step 2



A mixture of 0.15 g (0.79 mmol) of the product of Step 1, above, 0.098 g (0.79 mmol) of 4-fluorobenzaldehyde, 20 mg of 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide and 0.05 g (0.39 mmol) of triethyl amine was heated to 80°C for 3 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated in vacuo. The product was purified by medium pressure liquid chromatography over silica gel to give the product.

H^1-NMR ($CDCl_3$, 300 MHz):1.17 (s, 9H); 2.82 (dd, 1H); 3.67 (dd, 1H); 5.04 (dd, 1H); 7.06 (t, 2H); 7.19 (d, 2H); 7.97 (dd, 2H); 8.50 (d, 2H).

Step 3

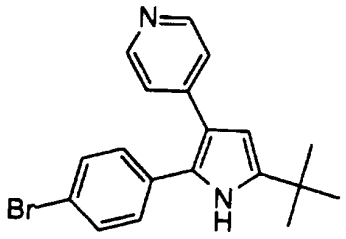


The product of Step 2 was dissolved in 1.0 mL of acetic acid (AcOH) and was treated with 0.5 g of ammonium acetate. The reaction mixture was heated to 110°C for 1 hour. The reaction mixture was cooled to room temperature and diluted with 25 mL of ethyl acetate and was washed with 3 x 10 mL of water and 1 x 10 mL of brine. The organic phase was dried over $MgSO_4$, filitered and concentrated in vacuo. The residue was purified by rotary chromatography over

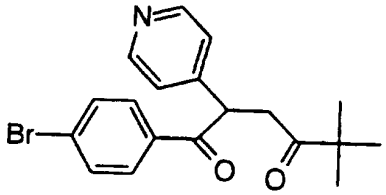
silica gel eluting with 2% MeOH/CH_2Cl_2.

H^1-NMR ($CDCl_3$, 300 MHz): 1.35 (2, 9H); 6.19 (d, 1H); 7.05 (t, 2H); 7.20, m, 2H); 7.25-7.36 (m, 2H); 8.03, bs, 1H); 8.41 (d, 2H).

PREPARATIVE EXAMPLE 3

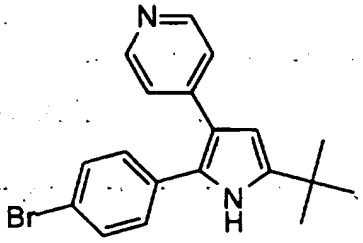


Step 1



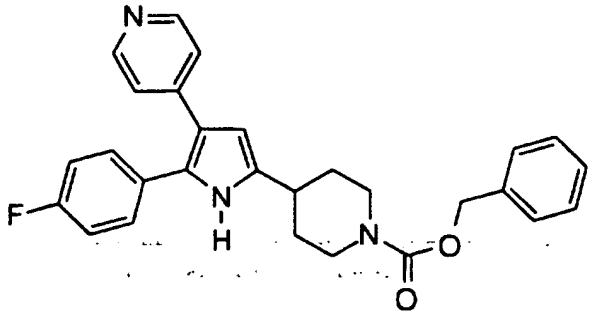
A mixture of 1 equivalent of the product of step 1 of Preparative Example 2 and 1 equivalent of 4-bromobenzaldehyde is dissolved in anhydrous ethanol. The solution is treated with 0.1 equivalents of 3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide and 0.5 equivalents of triethylamine. The mixture is heated to 80°C for 4 hours, then diluted with water and extracted with ethyl acetate (EtOAc). The combined organic extracts are washed with brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo to provide the product. The product is purified by flash chromatography over silica gel.

Step 2



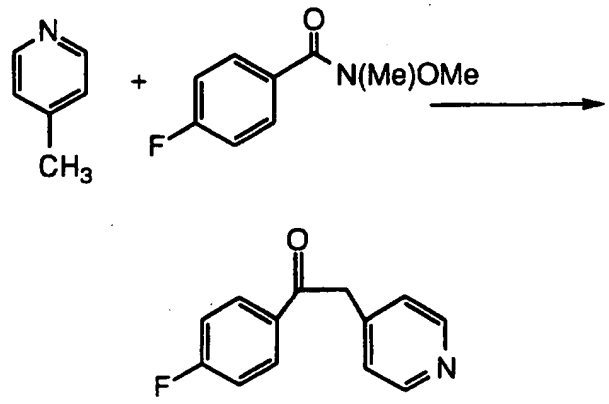
The product of Step 2 is treated with ammonium acetate as described above in Preparative Example 1.

PREPARATIVE EXAMPLE 4



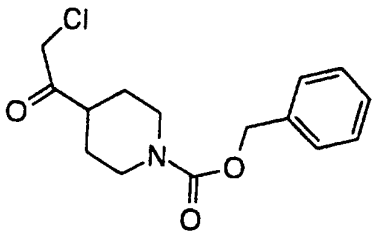
Step 1

1-(4-fluorophenyl)-2-(4-pyridyl)ethanone



To a solution of lithium diisopropyl amide (Aldrich Chemical Co. 2.0 M in heptane,THF ethyl benzene) 5.0 mL (10.0 mmol) in 12 mL of anhydrous THF at -78°C under nitrogen was added 0.93 g (10.0 mmol) of 4-picoline dropwise. The reaction mixture was stirred for 20 minutes and then treated with a solution of 2.0 g (10.0 mmol) of N-methyl-N-methoxy-4-fluorobenzamide in THF. The reaction mixture was warmed to 0°C and quenched by the addition of 20 mL of brine. The mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic phases were dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated in vacuo to give the title compound as an orange solid.

Step 2



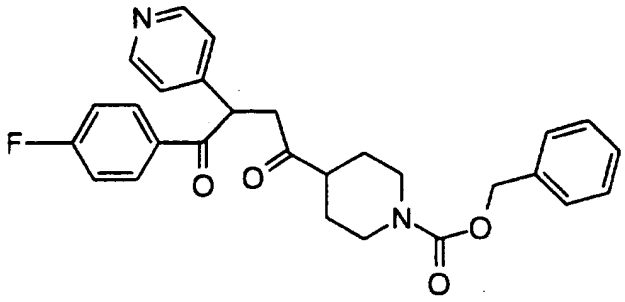
To a solution of N-carboxybenzyl-piperidine-4 carboxylic acid (5.0 g (19 mmol)) in 20 ml of dry EtOAc at -15°C was added 2.71 g (20.9 mmol) of diisopropylethylamine followed by 2.51 g (20 .9 mmol) of isopropenylchloroformate. The reaction mixture was stirred for 1 hour and filtered through a dry sintered funnel into a dry 250 ml round bottom flask at 0°C. The filtrate was treated with ethereal diazo methane (freshly prepared in the normal manner from 10 g of N-methylnitroso urea). The reaction mixture was stirred for 1 hour and then poured into 50 ml of water. The reaction mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic phases were washed with brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromato-

graphy over silica gel eluting with 50% EtOAc/hexanes to give the intermediate diazomethyl ketone. The material was dissolved in 20 ml of ether and cooled to 0°C and then treated portionwise with 10 ml of 1M HCl in ether.

After 1 hour the reaction mixture was poured into 20 ml of saturated $NaHCO_3$ solution: The product was extracted with EtOAc (3 x 20 ml). The combined organic phases were washed with brine and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 30% EtOAc/hexanes to give the desired product.

H^1-NMR ($CDCl_3$, 300 MHz): 1.56 (m, 2H); 1.85 (bm, 2H); 2.87 (m, 3H); 4.12 (s, 2H); 4.20 (bs, 1H); 5.12 (bs, 2H); 7.35 (m, 5H).

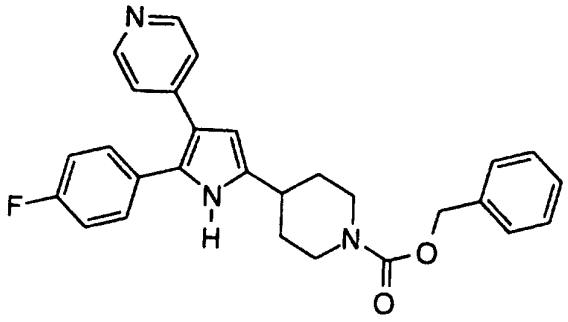
Step 3



To a solution of the product of Step 1 (0.13 g (0.67 mmol)) in 1.5 ml of dry DMSO was added 0.74 ml (0.67 mmol) of a 1M solution of sodium hexamethyl disilazide in THF. After 10 minutes a solution of 0.19 g (0.67 mmol) of the product of Step 2 was added in 1 ml DMSO dropwise. The reaction mixture was stirred for 2 hours, diluted with EtOAc (20 ml) and washed with water (3 x 10 ml). The combined organic phases were washed with brine and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by MPLC over silica gel eluting with 2% $MeOH/CH_2Cl_2$ to give the desired product.

H^1-NMR ($CDCl_3$, 300 MHz): 2.51 (m, 2H); 1.75 (bdd, 2H); 2.52 (m, 1H); 2.72 (dd, 1H); 2.85 (bm, 2H); 3.61 (dd, 1H); 4.12 (bs, 2H); 5.10 (s, 2H); 5.11 (dd, 1H); 7.19 (dd, 2H); 7.25-7.50 (m, 6H); 7.75 (d, 2H); 7.91 (d, 2H); 8.49 (d, 2H).

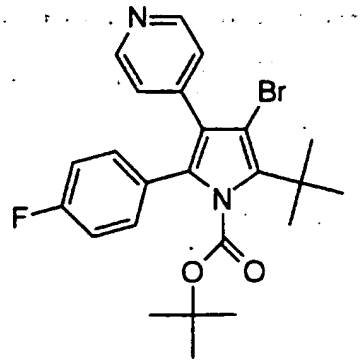
Step 4



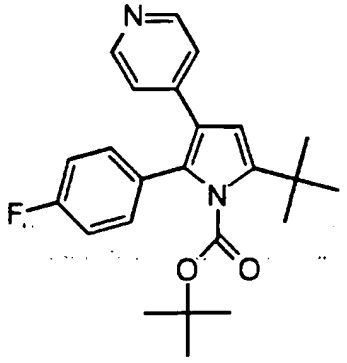
0.13 g (0.29 mmol) of the product of Step 3 was heated in 2 ml of acetic acid in the presence of 0.5 g ammonium acetate at 110°C for 2 hours. The reaction mixture was diluted with EtOAc (10 mL) and washed with water. The combined organic phases were washed with brine and dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by rotory chormatography over silica gel eluting with 5% $MeOH/CH_2Cl_2$ to give the desired product.

H^1-NMR ($CDCl_3$, 300 MHz):1.67 (m, 2H); 2.02 (bd, 2h); 2.75-3.0 (m, 3H); 4.29 bd, 2H); 5.12 (s, 2H); 6.19 (d, 1H); 7.27 (d, 2H); 7.28-7.39 (m, 7H); 8.36 (d, 2H); 8.51 (bs, 2H); 8.65 (bs, 1H). FAB ms: C28H27N3O2:437; Observed: 438 (M^++1).

PREPARATIVE EXAMPLE 5

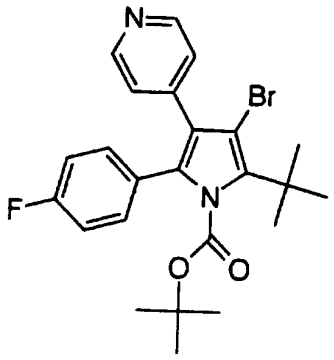


Step 1



To 1 equivalent of the product of Preparative Example 2 in THF is added 1.1 equivalents of t-butyloxycarbonyl anhydride, 1 equivalent of triethylamine and 0.1 equivalents of dimethylaminopyridine. The reaction mixture is stirred until the starting material was consumed. The solution is partititioned between ethyl acetate and water. The organic phase is washed with water and brine and is dried over $MgSO_4$. The solution is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel.

Step 2

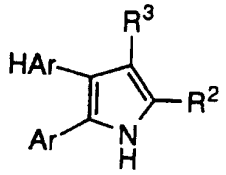


To a solution of the product of Step 1 in THF at -78°C is added 1.05 equivalents of N-bromosuccinimide. The mixture is allowed to stir as the temperature is increased to 0°C over 1 hour. After the starting material is consumed the reaction mixture is diluted with ethyl acetate and washed with sodium bisulfite followed by water and brine. The organic phase is dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by chromatography over silica gel to produce the desired product.

PREPARATIVE EXAMPLES 6-54

Employing the procedures described above, the preparative compounds described in Table I can be synthesized.

TABLE I

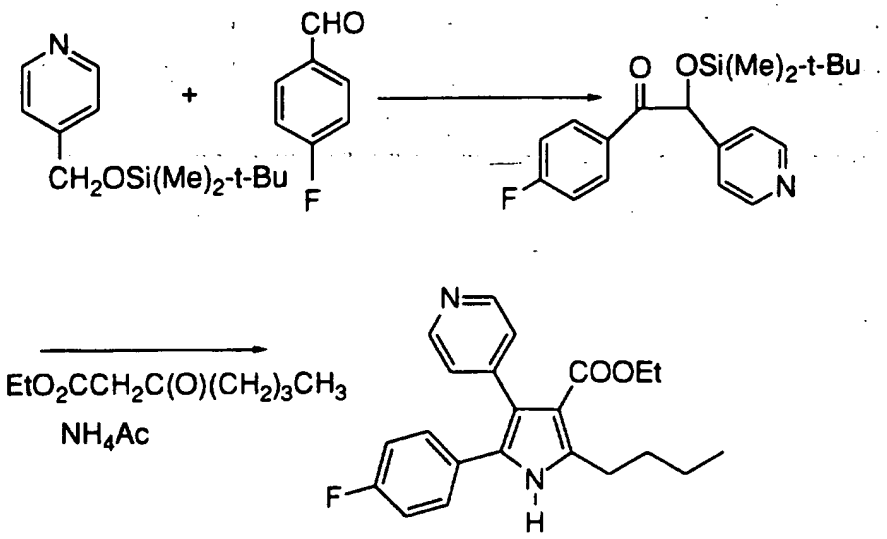


Preparative Example	R^2	Ar	HAr	R^3
6	t-butyl	Ph-4-F	3-methyl-4-pyridyl	H

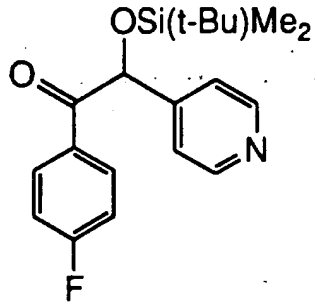
7	t-butyl	Ph-4-F	4-quinolinyl	H
8	t-butyl	Ph-4-F	2-quinolinyl	H
9	t-butyl	Ph-4-F	2-pyrimidinyl	H
10	t-butyl	Ph-4-F	4-pyrimidinyl	H
11	t-butyl	Ph-4-F	3-pyridazinyl	H
12	t-butyl	Ph-4-F	2-pyrazinyl	H
13	t-butyl	Ph-4-F	2-pyrimidinyl	H
14	t-butyl	Ph-4-F	4-pyrimidinyl	H
15	t-butyl	Ph-4-F	2-imidazo-(4,5-b)-pyridinyl	H
16	i-butyl	Ph-4-F	4-Pyridyl	H
17	4-N-Me-piperidine	Ph-4-F	4-Pyridyl	H
18	4-N-Bn-piperidine	Ph-4-F	4-Pyridyl	H
19	4-N-Ph-piperidinyl	Ph-4-F	4-Pyridyl	H
20	CH_2-4-(N-Me)-piperazinyl	Ph-4-F	4-Pyridyl	H
21	4-N-Me-piperidine	Ph-4-F	4-Pyridyl	H
22	4-N-Me-piperidine	Ph-4-Cl	4-Pyridyl	H
23	4-N-Me-piperidine	Ph	4-(2-Me)-pyridyl	H
24	4-N-Me-piperidine	Ph	4-Pyridyl	H
25	t-butyl	Ph-2-OMe	4-Pyridyl	H
26	t-butyl	Ph-3-OMe	4-Pyridyl	H
27	t-butyl	Ph-4-OMe	4-Pyridyl	H
28	t-butyl	Ph-4-(4-N-$COCH_3$)-piperazinyl	4-Pyridyl	H
29	t-butyl	Ph-4-morpholinyl	4-Pyridyl	H
30	t-butyl	Ph-4-Cl	4-Pyridyl	H
31	t-butyl	Ph-3-Cl	4-Pyridyl	H
32	t-butyl	Ph-3,4-Cl	4-Pyridyl	H
33	t-butyl	Ph-3-CF_3	4-Pyridyl	H

34	t-butyl	Ph-4-S-Me	4-Pyridyl	H
35	t-butyl	Ph-4-S(O)-Me	4-Pyridyl	H
36	4-piperidine	Ph-4-F	4-Pyridyl	H
37	3-N-Me-piperidinyl	Ph-4-F	4-Pyridyl	H
38	CH2-morpholinyl	Ph-4-F	4-Pyridyl	H
39	4-N-Me-piperidine	Ph	4-Pyridyl	Br
40	4-N-Me-piperidine	Ph	4-Pyridyl	Cl
41	4-N-Me-piperidine	Ph	4-Pyridyl	NO_2
42	4-N-Me-piperidine	Ph	4-Pyridyl	CH_2OH
43	t-butyl	Ph-4-NO_2	4-Pyridyl	H
44	t-butyl	Ph-4-NMe_2	4-Pyridyl	H
45	t-butyl	Ph-2-Cl	4-Pyridyl	H
46	4-piperidine	Ph-4-F	4-Pyridyl	H
47	t-butyl	Ph-4-F	2-pyridyl	H
48	t-butyl	Ph-4-F	2-methyl-4-pyridyl	H
49	t-butyl	Ph-4-F	3-methyl-4-pyridyl	H
50	cyclohexyl	Ph-4-F	4-Pyridyl	H
51	i-propyl	Ph-4-F	4-Pyridyl	H
52	1-cyclopropyl-ethyl	Ph-4-F	4-Pyridyl	H
53	t-butyl	Ph-4-F	2,4-dimethylpyridyl	H
54	t-butyl	Ph-4-F	2,6-dimethylpyridyl	H

EXAMPLE 1



Step 1

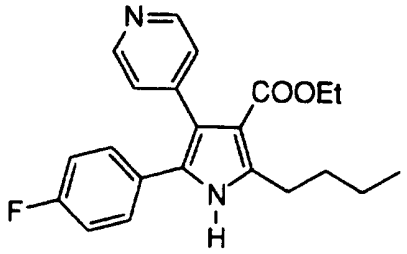


To a 2 liter 3-neck flask equipped with a mechanical stirrer under N_2 was added 54.6 g (0.59 m) of diisopropylethylamine and 150 mL of THF. The solution was cooled to -20°C and treated with 268 mL (0.67 m) of 2.5 M butyl lithium over 20 min. To the reaction mixture was added 125 g (0.56 m) of 4-(t-butyldimethylsilyloxymethyl) pyridine in 100 mL of THF over 30 min. The reaction mixture was stirred for 1 hr. at -15°C and then treated with a solution of 108 g (0.59m) of 4-fluorobenzaldehyde dissolved in 100 mL of THF dropwise. The reaction was warmed to 0°C and stirred for 1 hr, then was warmed to room temperature and the reaction quenched by the addition of 1 L of 20%

NH_4Cl solution. The aqueous phase was extracted with EtOAc (3 x 500 mL).

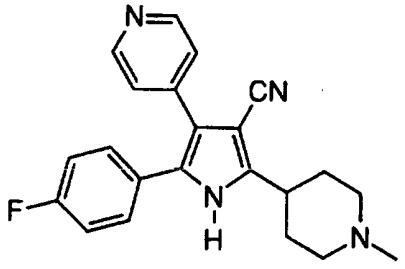
The combined organic phases were washed with water (1 x 500 mL), 1 x 500 mL brine and were dried over $MgSO_4$. The mixture was filtered and the filtrate was concentrated in vacuo to give a dark oil. The product was purified by flash chromatography over silica gel eluting with 10-20% EtOAc/hexanes.

Step 2



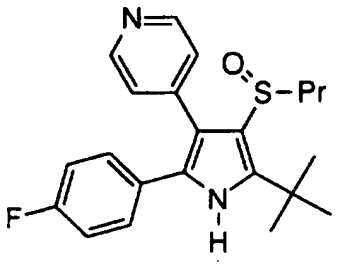
A mixture of ethyl 3-keto-heptanoate, 0.7 equivalents of the product of Step 1 and 4 equivalents of ammonium acetate are heated in acetic acid at reflux until the benzoin is consumed. The reaction mixture is diluted with ethyl acetate and washed with water and brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 2



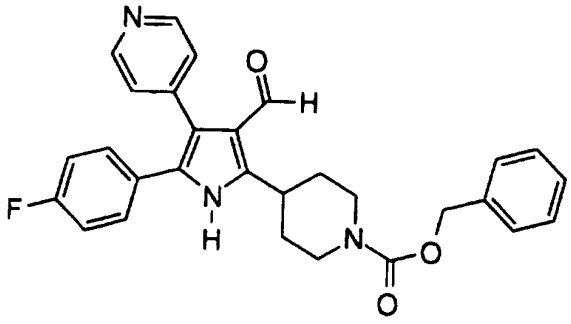
A mixture of 1-(4-N-methylpiperidinyl)-2-cyanoethanone, 0.7 equivalents of the reaction product of Example 1, Step 1, and 4 equivalents of ammonium acetate are heated in acetic acid at reflux until the benzoin is consumed. The reaction mixture is diluted with EtOAc and washed with water and brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 3



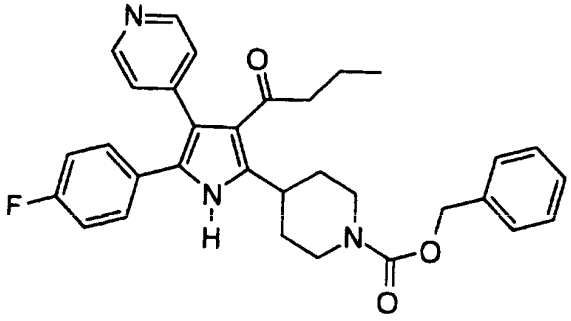
The product of Preparative Example 2 is dissolved in methylene chloride and treated with 1.05 equivalents of n-propylsulfinyl chloride at 0°C under nitrogen. After 30 minutes triethylamine is added to neutralize the reaction mixture. The reaction mixture is diluted with ethyl acetate and washed with water and brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 4



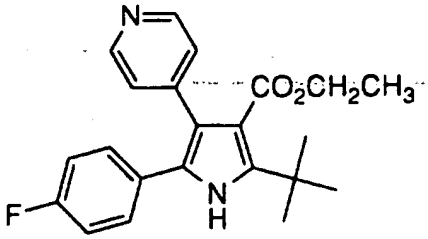
To 5 ml of DMF at room temperature under nitrogen is added 0.3 g (2 mmol) of $POCl_3$ dropwise. After 15 minutes a solution of 0.37 g (0.86 mmol) of the product of Preparative Example 4 is added dropwise. The solution was warmed at 60°C until the starting material had been consumed. The reaction mixture was cooled to room temperature and then poured into ice water (20 ml). The mixture was made basic by addition of saturated sodium carbonate solution and then stirred in the presence of 20 mL of chloroform. The chloroform phase was separated and the aqueous phase was extracted with chloroform (2 x 10 mL). The combined organic phase is washed with water and brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo and the residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 5



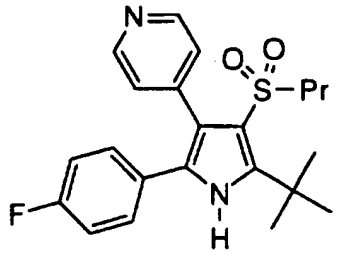
To 5 ml of N,N-dimethyl-butyramide at room temperature under nitrogen is added 0.3 g (2 mmol) of $POCl_3$ dropwise. After 15 minutes a solution of 0.37 g (0.86 mmol) of the product of Preparative Example 4 is added dropwise. The solution is warmed at 60°C until the starting material had been consumed. The reaction mixture is cooled to room temperature and then poured into ice water (20 ml). The mixture is made basic by addition of saturated sodium carbonate solution and then stirred in the presence of 20 mL of chloroform. The chloroform phase is seperated and the aqueous phase extracted with chloroform (2 x 10 ml). The combined organic phase is washed with water and brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo. The residue is purified by chromatography over silica gel to give the desired product.

EXAMPLE 6



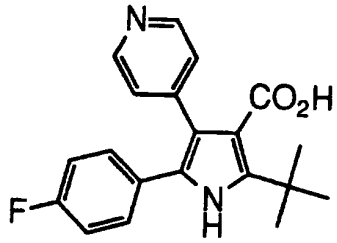
Using the procedure set forth in Example 1, substitute $EtO_2CCH_2C(O)C(CH_3)_3$ for $EtO_2CCH_2C(O)(CH_2)_3CH_3$ to produce the desired compound.

EXAMPLE 7



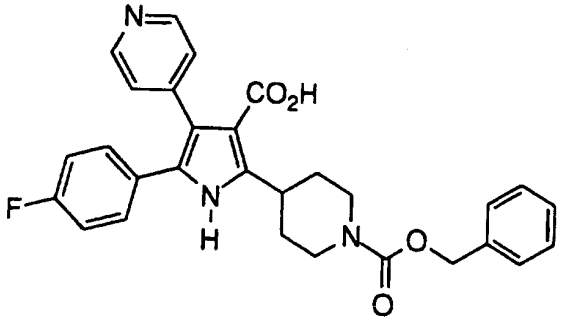
The product of Example 3 is reacted with 1.05 equivalents of meta-chloroperoxybenzoic acid in CH_2Cl_2 at 0°C. The reaction mixture is stirred overnight at room temperature. The solution is diluted with EtOAc and washed with saturated sodium bicarbonate solution followed by brine. The solution is dried over MgSO4, filtered and concentrated in vacuo. The residue is purified by silica gel chromatography to produce the desired product.

EXAMPLE 8



The product of Example 6 is heated with excess lithium hydroxide in DME/water at reflux until the conversion to the acid is complete. The reaction mixture is acidified with acetic acid and extracted with ethyl acetate to give the desired product.

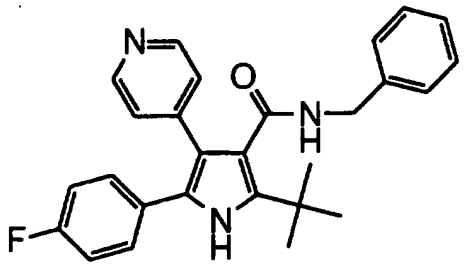
EXAMPLE 9



The product of Example 4 is dissovled in t-butyl alcohol and methyl 2- butene (6:1 ratio). The solution is then treated with 1.5

eq of monobasic sodium phosphate and an aqueous solution of sodium chlorate. The reaction mixture is stirred at room temperature until the sm is consumed. The pH is adjusted to 5.5 with dilute HCl. The product is extracted with ethyl acetate and the combined organic phase is washed with water and brine and dried over $MgSO_4$. The mixture is filtered and the filtrate is concentrated in vacuo to give the desired product.

EXAMPLE 10

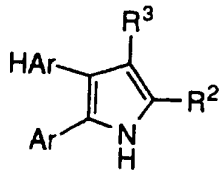


The product of Example 8 is dissolved in DMF and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, benzyl amine and Hunigs base and a catalytic amount of DMAP. The mixture is stirred overnight at room temperature. The solution is diluted with water and extracted with ethyl acetate. The organic phase is washed with water and brine and is dried over $MgSO_4$, filtered and concentrated in vacuo. The residue is purified by chromatography.

EXAMPLES 11-66

Employing the procedures described above, additional example of compoounds of Formulal are described in Table II.

TABLE II



Example	R^2	Ar	HAr	R^3
11	t-butyl	Ph-4-F	3-methyl-4-pyridyl	CN
12	t-butyl	Ph-4-F	3-methyl-4-pyridyl	COMe
13	t-butyl	Ph-4-F	3-methyl-4-pyridyl	CONHMe
14	t-butyl	Ph-4-F	3-methyl-4-pyridyl	SO_2Et
15	t-butyl	Ph-4-F	3-methyl-4-pyridyl	COOEt
16	t-butyl	Ph-4-F	4-quinolinyl	CN
17	t-butyl	Ph-4-F	2-quinolinyl	CN
18	t-butyl	Ph-4-F	2-pyrimidinyl	CN
19	t-butyl	Ph-4-F	4-pyrimidinyl	CN
20	t-butyl	Ph-4-F	3-pyridazinyl	CN
21	t-butyl	Ph-4-F	2-pyrazinyl	CN
22	t-butyl	Ph-4-F	2-pyrimidinyl	CN
23	t-butyl	Ph-4-F	4-pyrimidinyl	CN
24	t-butyl	Ph-4-F	2-imidazo-(4,5-b)-pyridinyl	CN
25	t-butyl	Ph-4-F	4-(2-amino)-pyridyl	CN
26	t-butyl	Ph-4-F	4-(2-N-benzyl-amino)-pyridyl	CN
27	t-butyl	Ph-4-F	4-(2-acetylamino)-pyridyl	COMe
28	t-butyl	Ph-4-F	4-pyridyl	CN

29	t-butyl	Ph-4-F	4-pyridyl	SO_2Pr
30	t-butyl	Ph-4-F	4-pyridyl	CONH -iBu
31	t-butyl	Ph-4-F	4-pyridyl	COMe
32	i-butyl	Ph-4-F	4-pyridyl	CN
33	4-N-Me-piperidinyl	Ph-4-F	4-pyridyl	COMe
34	4-N-Bn-piperidinyl	Ph-4-F	4-pyridyl	COMe
35	4-N-Ph-piperidinyl	Ph-4-F	4-pyridyl	COMe
36	CH_2-4-(N-Me)-piperazinyl	Ph-4-F	4-pyridyl	CN
37	4-N-Me-piperidinyl	Ph-4-F	4-pyridyl	CN
38	4-N-Me-piperidinyl	Ph-4-Cl	4-pyridyl	CN
39	4-N-Me-piperidinyl	Ph	4-(2-Me)-pyridyl	CN
40	4-N-Me-piperidinyl	Ph	4-pyridyl	CN
41	t-butyl	Ph-2-OMe	4-pyridyl	CN
42	t-butyl	Ph-3-OMe	4-pyridyl	CN
43	t-butyl	Ph-4-OMe	4-pyridyl	CN
44	t-butyl	Ph-4-(4-N-$COCH_3$)-piperazinyl	4-pyridyl	CN
45	t-butyl	Ph-4-morpholinyl	4-pyridyl	CN
46	t-butyl	Ph-4-Cl	4-pyridyl	CN
47	t-butyl	Ph-3-Cl	4-pyridyl	CN
48	t-butyl	Ph-3,4-Cl	4-pyridyl	CN
49	t-butyl	Ph-3-CF_3	4-pyridyl	CN
50	t-butyl	Ph-4-S-Me	4-pyridyl	CN
51	t-butyl	Ph-4-S(O)-Me	4-pyridyl	CN
52	4-piperidine	Ph-4-F	4-pyridyl	CN
53	3-N-Me-piperidinyl	Ph-4-F	4-pyridyl	CN

54	CH2-morpholinyl	Ph-4-F	4-pyridyl	CN
55	t-butyl	Ph-4-NO_2	4-pyridyl	CN
56	t-butyl	Ph-4-NMe_2	4-pyridyl	CN
57	t-butyl	Ph-2-Cl	4-pyridyl	CN
58	4-piperidinyl	Ph-4-F	4-pyridyl	CN
59	t-butyl	Ph-4-F	2-pyridyl	CN
60	t-butyl	Ph-4-F	2-methyl-4-pyridyl	CN
61	t-butyl	Ph-4-F	3-methyl-4-pyridyl	CN
62	cyclohexyl	Ph-4-F	4-pyridyl	CN
63	i-propyl	Ph-4-F	4-Pyridyl	CN
64	1-cyclopropyl-ethyl	Ph-4-F	4-pyridyl	CN
65	t-butyl	Ph-4-F	2,4-dimethylpyridyl	CN
66	t-butyl	Ph-4-F	2,6-dimethylpyridyl	CN

BIOLOGICAL ASSAYS

The ability of compounds of the present invention to inhibit the synthesis or the activity of cytokines can be demonstrated using the following *in vitro* assays.

Lipopolysaccharide mediated production of cytokines

Human peripheral blood mononuclear cells (PBMC) are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* **151,** 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium-heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2 x 10^6 cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin

(10 U/mL) and 0.05% DMSO. Lipopolysaccharide (Salmonella type Re545; Sigma Chemicals) is added to the cells to a final concentration of 100 ng/mL. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the test compound, at the appropriate dilution, and are incubated for 24 hours at 37°C in 5% CO_2 . At the end of the culture period, cell-culture supernatants are assayed for IL-1β , TNF-α, IL-6 and PGE_2 production using specific ELISA.

IL-1 mediated cytokine production

Human peripheral blood mononuclear cells are isolated from fresh human blood according to the procedure of Chin and Kostura, *J. Immunol.* **151,** 5574-5585 (1993). Whole blood is collected by sterile venipuncture into 60 mL syringes coated with 1.0 mL of sodium- heparin (Upjohn, 1000 U/mL) and diluted 1:1 in Hanks Balanced Salt Solution (Gibco). The erythrocytes are separated from the PBMC's by centrifugation on a Ficoll-Hypaque lymphocyte separation media. The PBMC's are washed three times in Hanks Balanced Salt Solution and then resuspended to a final concentration of 2×10^6 cell/mL in RPMI containing 10% fresh autologous human serum, penicillin streptomycin (10 U/mL) and 0.05% DMSO. Endotoxin free recombinant human IL-1β is then added to a final concentration of 50 pMolar. An aliquot (0.1 mL) of the cells is quickly dispensed into each well of a 96 well plate containing 0.1 mL of the compound at the appropriate dilution. and are incubated for 24 hours. at 37°C in 5% CO_2 . At the end of the culture period, cell culture supernatants are assayed for TNF-α, IL-6 and PGE_2 synthesis using specific ELISA.

Determination of IL-1β , TNF-α, IL-6 and prostanoid production from LPS or IL-1 stimulated PBMC's

IL-1β ELISA

Human IL-1β can be detected in cell-culture supernatants or whole blood with the following specific trapping ELISA. Ninety-six well

plastic plates (Immulon 4; Dynatech) are coated for 12 hours at 4°C with 1 mg/mL protein-A affinity chromatography purified mouse anti-human IL-1b monoclonal antibody (purchased as an ascites preparation from LAO Enterprise, Gaithersburg Maryland.) diluted in Dulbecco's phosphate-buffered saline (-$MgCl_2$, -$CaCl_2$). The plates are washed with PBS-Tween (Kirkegaard and Perry) then blocked with 1% BSA diluent and blocking solution (Kirkegaard and Perry) for 60 minutes at room temperature followed by washing with PBS Tween. IL-1β standards are prepared from purified recombinant IL-1β produced from E. *coli*. The highest concentration begins at 10 ng/mL followed by 11 two-fold serial dilutions. For detection of IL-1β from cell culture supernatants or blood plasma, 10 - 25 mL of supernatant is added to each test well with 75 - 90 mL of PBS Tween. Samples are incubated at room temperature for 2 hours then washed 6 times with PBS Tween on an automated plate washer (Dennly). Rabbit anti-human IL-1β polyclonal antisera diluted 1:500 in PBS-Tween is added to the plate and incubated for 1 hour at room temperature followed by six washes with PBS-Tween. Detection of bound rabbit anti-IL-1β IgG is accomplished with Fab' fragments of Goat anti-rabbit IgG-horseradish peroxidase conjugate (Accurate Scientific) diluted 1:10,000 in PBS-Tween. Peroxidase activity was determined using TMB peroxidase substrate kit (Kirkegaard and Perry) with quantitation of color intensity on a 96-well plate Molecular Devices spectrophotometer set to determine absorbance at 450 nM. Samples are evaluated using a standard curve of absorbance versus concentration. Four-parameter logistics analysis generally is used to fit data and obtain concentrations of unknown compounds.

TNF-α ELISA

Immulon 4 (Dynatech) 96-well plastic plates are coated with a 0.5 mg/mL solution of mouse anti-human TNF-α monoclonal antibody. The secondary antibody is a 1:2500 dilution of a rabbit anti-human TNF-α polyclonal serum purchased from Genzyme. All other operations are identical to those described above for IL-1b. The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven

2 fold dilutions are made beginning at 20 ng/mL TNF-α.

IL-6 ELISA

Levels of secreted human IL-6 are also determined by specific trapping ELISA as described previously in Chin and Kostura, *J. Immunol.* **151,** 5574-5585 (1993). (Dynatech) ELISA plates are coated with mouse anti-human IL-6 monoclonal antibody diluted to 0.5 mg/ml in PBS. The secondary antibody, a rabbit anti-human IL-6 polyclonal antiserum, is diluted 1:5000 with PBS-Tween. All other operations are identical to those described above for IL-1β. The standards are prepared in PBS-Tween + 10% FBS or HS. Eleven 2 fold dilutions are made beginning at 50 ng/mL IL-6.

PGE2 production

Prostaglandin E2 is detected in cell culture supernatants from LPS or IL-1 stimulated PBMC's using a commercially available enzyme immunoassay . The assay purchased from the Cayman Chemical (Catalogue number 514010) and is run according to the manufacturers instructions.

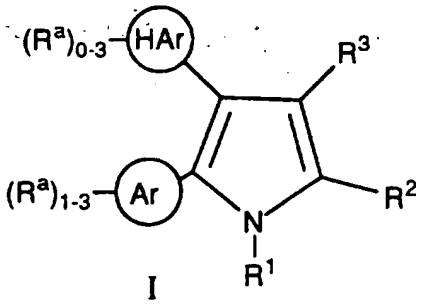
Interleukin8 (IL-8)

The present compounds can also be assayed for IL-8 inhibitory activity as discussed below. Primary human umbilical cord endothelial cells (HUVEC) (Cell Systems, Kirland, Wa) are maintained in culture medium supplemented with 15% fetal bovine serum and 1% CS-HBGF consisting of aFGF and heparin. The cells are then diluted 20-fold before being plated (250 µl) into gelatin coated 96-well plates. Prior to use, culture medium is replaced with fresh medium (200µl). Buffer or test compound (25µl, at appropriate concentrations) is then added to each well in quadruplicate wells and the plates incubated for 6h in a humidified incubator at 37°C in an atmosphere of 5% CO_2. At the end of the

incubation period, supernatant is removed and assayed for IL-8 concentration using an IL-8 ELISA kit obtained from R&D Systems (Minneapolis, MN). All data is presented as mean value (ng/ml) of multiple samples based on the standard curve. IC_{50} values where appropriate can be generated by non-linear regression analysis.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

(Ar) represents a C_{5-10} aryl group substituted with 1 - 3 groups selected from R^a;

(HAr) represents a heteroaryl group containing from 5 to 10 atoms, 1-3 of which are heteroatoms, 0-3 of which heteroatoms are N and 0-1 of which are O or S, said heteroaryl group being unsubstituted or substituted with 1 -3 R^a groups;

each R^a independently represents a member selected from the group consisting of: halo; CN, NO_2, R^{21}; OR^{23}; SR^{23}; $S(O)R^{21}$; SO_2R^{21}; $NR^{20}R^{23}$; $NR^{20}COR^{21}$; $NR^{20}CO_2R^{21}$; $NR^{20}CONR^{20}R^{23}$; $NR^{20}SO_2R^{21}$; $NR^{20}C(NR^{20})NHR^{23}$, CO_2R^{23}; $CONR^{20}R^{23}$; $SO_2NR^{20}R^{23}$; $SO_2NR^{20}COR^{21}$; $SO_2NR^{20}CONR^{20}R^{23}$; $SO_2NR^{20}CO_2R^{21}$; $OCONR^{20}R^{23}$; $OCONR^{20}SO_2R^{20}$; $C(NR^{20})NR^{20}R^{23}$; $CONR^{20}SO_2R^{21}$; $SO_2NR^{20}CO_2R^{21}$ and tetrazol-5-yl;

R^1 is selected from the group consisting of: H; C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, aryl and heterocyclyl, said alkyl, alkenyl,

aryl, alkynyl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: aryl, heteroaryl, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{21}$, SO_2R^{21}, $SO_2NR^{20}R^{23}$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CONR^{20}R^{23}$, $NR^{20}COR^{21}$, $NR^{20}CO_2R^{21}$, $NR^{20}CONR^{20}R^{23}$, $N(R^{20})C(NR^{20})NHR^{23}$, CO_2R^{23}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$, $NR^{20}SO_2R^{21}$, $SO_2NR^{20}CO_2R^{21}$, $OCONR^{20}R^{23}$, $OCONR^{20}SO_2R^{21}$, $C(O)OCH_2OC(O)R^{20}$ and $OCONR^{20}R^{23}$;

R^2 is selected from the group consisting of: heterocyclyl; C_{1-15} alkyl, C_{2-15} alkenyl, and C_{2-15} alkynyl, said alkyl, alkenyl and alkynyl groups being optionally interrupted by 1-2 oxo groups or heteroatoms selected from O, S, S(O), SO_2 or NR^{24}; said alkyl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from 1-3 of halo, aryl, aryl$(R^a)_2$, heteroaryl, OR^{20}, SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $C(O)R^{22}$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}C(O)NR^{20}R^{21}$, $NR^{20}C(O)NHR^{21}$, $NR^{20}C(O)R^{21}$, $N(R^{22})C(NR^{22})NHR^{22}$, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$ and $OCONR^{20}R^{23}$;

R^3 is selected from the group consisting of: CN, $S(O)R^{21}$, SO_2R^{21}, COR^{20}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{21}$, $SO_2NR^{20}CON(R^{20})_2$, CO_2R^{20}, $CONR^{20}R^{23}$, $CONR^{20}SO_2R^{21}$ and $SO_2NR^{20}CO_2R^{21}$;

R^{20} represents a member selected from the group consisting of: H, C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

R^{21} represents a member selected from the group consisting of: C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, optionally interrupted by 1-2 heteroatoms selected from O, S, S(O), SO_2 or NR^{24}; heterocyclyl, aryl and heteroaryl;

said alkyl, alkenyl, alkynyl, heterocyclyl, aryl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, aryl, heteroaryl, CN, OR^{20}, $O((CH_2)_nO)_mR^{20}$, $NR^{20}((CH_2)_nO)_mR^{20}$ wherein n represents an integer of from 2 to 4, and m represents an integer of from 1 to 3; SR^{20}, $N(R^{20})_2$, $S(O)R^{22}$, SO_2R^{22}, $SO_2N(R^{20})_2$, $SO_2NR^{20}COR^{22}$, $SO_2NR^{20}CON(R^{20})_2$, $NR^{20}COR^{22}$, $NR^{20}CO_2R^{22}$, $NR^{20}CON(R^{20})_2$, $NR^{22}C(NR^{22})NHR^{22}$, CO_2R^{20}, $CON(R^{20})_2$, $CONR^{20}SO_2R^{22}$, $NR^{20}SO_2R^{22}$, $SO_2NR^{20}CO_2R^{22}$, $OCONR^{20}SO_2R^{22}$, $OCONHR^{20}R^{23}$ and $OCON(R^{20})_2$;

R^{22} is selected from the group consisting of: C_{1-15} alkyl, C_{3-15} alkenyl, C_{3-15} alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

R^{23} is R^{21} or H;

R^{24} is selected from aryl, COR^{22}, CO_2R^{22}, $CON(R^{20})_2$, R^{23} and SO_2R^{22};

and in a functional group substituent, when two R^{20} groups are present, when R^{20} and R^{21} are present, or when R^{20} and R^{23} are present, said two R^{20} groups, R^{20} and R^{21} or said R^{20} and R^{23} may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said hetercyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

2. A compound in accordance with claim 1 wherein: Ar is substituted phenyl.

3. A compound in accordance with claim 1 wherein: HAr is an optionally substituted:

a) pyridyl,
b) quinolyl,
c) purinyl,
d) imidazolyl or
e) imidazopyridine.

4. A compound in accordance with claim 1 wherein R^1 is:

a) H or
b) substituted or unsubstituted C_{1-15} alkyl.

5. A compound in accordance with claim 1 wherein: R^2 is:

a) C_{1-7} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$,

b) C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$,

c) C_{1-4} alkyl-aminoacyl-C_{2-6} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$,

d) C_{1-4} alkyl-aminoacyl-C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo, $N(R^{20})_2$ or NR^{24},

e) C_{1-4} alkyl-aminoacylamino-C_{2-6} alkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo or $N(R^{20})_2$, or

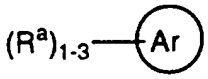
f) C_{1-4} alkyl-aminoacylamino-C_{4-7} cycloalkyl optionally interupted by 1 nitrogen atom and optionally substituted by oxo, $N(R^{20})_2$ or NR^{24};.

6. A compound in accordance with claim 1 wherein R^a is selected from the group consisting of: halo; CN, R^{21}; OR^{23}; CO_2R^{23}; $CONR^{20}R^{23}$ and tetrazol-5-yl.

7. A compound in accordance with claim 1 wherein: R^3 is selected from the group consisting of:

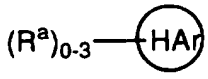
a) CO_2R^{20};
b) $CONR^{20}R^{23}$ and
c) CN.

8. A compound in accordance with claim 1 wherein:



is selected from the group consisting of:

a) phenyl,
b) 4-fluorophenyl,
c) 4-chlorophenyl,
d) 3-fluorophenyl,
e) 3-chlorophenyl,
f) 3-methylphenyl,
g) 3,4-dichlorophenyl, and
h) 3-hydroxyphenyl;



is selected from the group consisting of:

a) 4-pyridyl,
b) 4-(2-methylpyridyl),
c) 4-(2-aminopyridyl),
d) 4-(2-methoxypyridyl),
e) 4-quinolyl,
f) 4-pyrimidinyl,
g) 9-purinyl,
h) 7-(imidazo[4,5-b]pyridinyl), and
i) 4-(3-methylpyridyl);

R^1 is H;

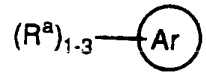
R^2 is selected from the group consisting of:

a) isopropyl,
b) tert-butyl,
c) phenethyl,
d) benzyl,
e) 2-amino-2,2-dimethylethyl,
f) 4-aminomethylbenzyl,
g) glycylaminomethyl,
h) (L)-alanylaminomethyl,
i) 2-amino-2,2-dimethylacetylaminomethyl,
j) N,N-dimethylaminoethyl-N-methylaminocarbonylaminomethyl,
k) 3-piperidinecarbonylaminomethyl,
l) 4-piperidinecarbonylaminomethyl,
m) piperidine-4-yl,
n) piperidine-3-yl,
o) pyrrolidin-3-yl,
p) N-methylpiperidine-4-yl,
q) N-benzylpiperidine-4-yl, or
r) N-(2-hydroxyeth-1-yl)piperidine-4-yl;
s) N-methanesulfonylpiperidine-4-yl

and R^3 is selected from the group consisting of:

a) CO_2R^{20};
b) $CONR^{20}R^{23}$ and
c) CN.

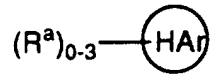
9. A compound in accordance with claim 1 wherein:



is selected from the group consisting of:

a) phenyl,
b) 4-fluorophenyl,

c) 4-chlorophenyl,
d) 3-fluorophenyl,
e) 3-chlorophenyl,
f) 3-methylphenyl,
g) 3,4-dichlorophenyl and
h) 3-hydroxyphenyl;


is selected from the group consisting of:

a) 4-pyridyl,
b) 4-(2-methylpyridyl),
c) 4-(2-aminopyridyl),
d) 4-(2-methoxypyridyl),
e) 4-quinolyl,
f) 4-pyrimidinyl,
g) 9-purinyl,
h) 7-(imidazo[4,5-b]pyridinyl), and
i) 4-(3-methylpyridyl);

R^1 is C_{1-15} alkyl;

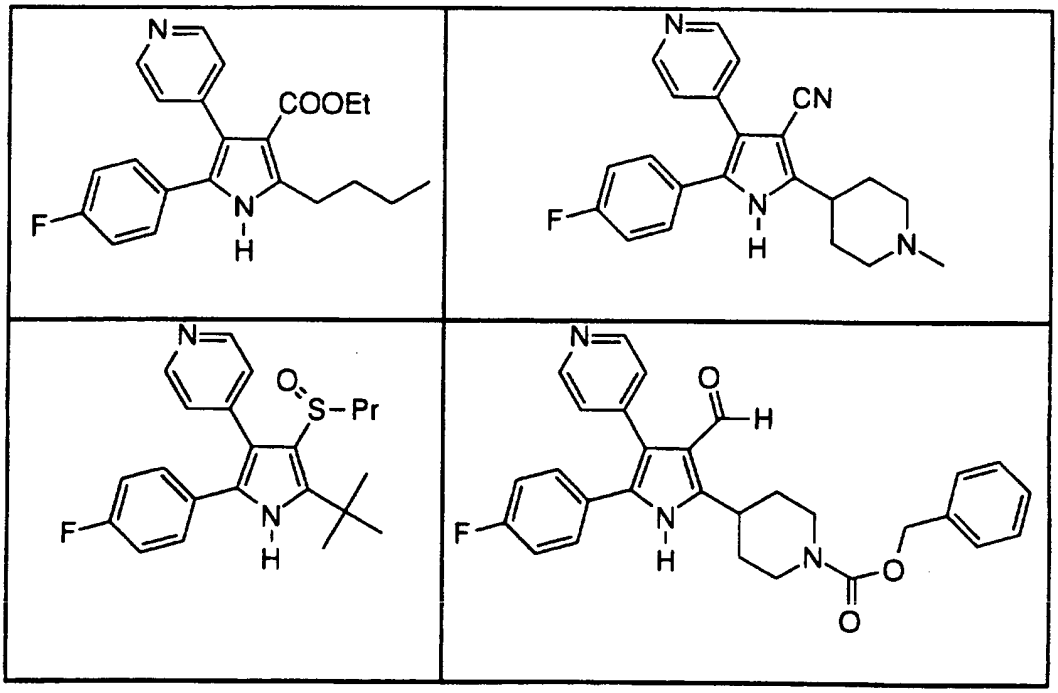
R^2 is selected from the group consisting of:

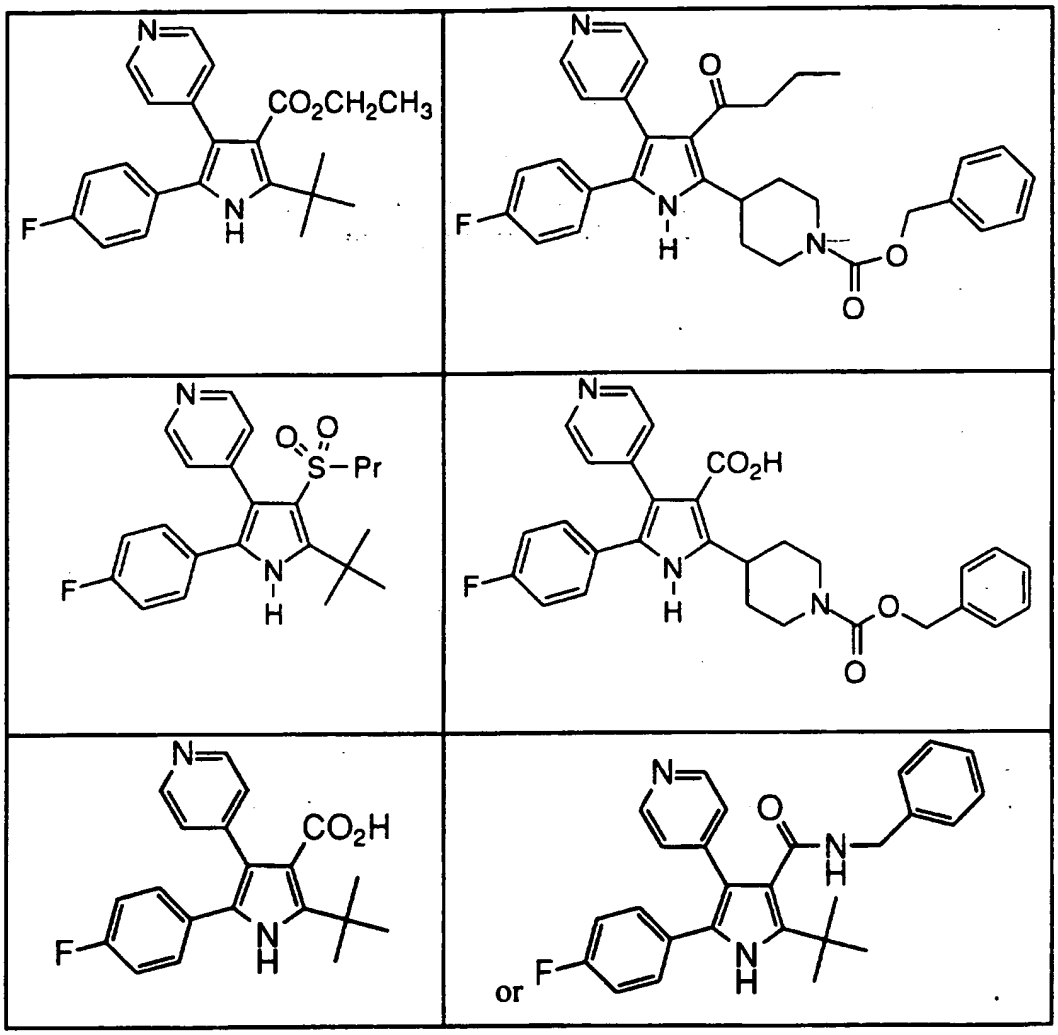
a) isopropyl,
b) tert-butyl,
c) phenethyl,
d) benzyl,
e) 2-amino-2,2-dimethylethyl,
f) 4-aminomethylbenzyl,
g) glycylaminomethyl,
h) (L)-alanylaminomethyl,
i) 2-amino-2,2-dimethylacetylaminomethyl,
j) N,N-dimethylaminoethyl-N-methylaminocarbonylaminomethyl,
k) 3-piperidinecarbonylaminomethyl,

l) 4-piperidinecarbonylaminomethyl,
m) piperidine-4-yl,
n) piperidine-3-yl,
o) pyrrolidin-3-yl,
p) N-methylpiperidine-4-yl,
q) N-benzylpiperidine-4-yl, or
r) N-(2-hydroxyeth-1-yl)piperidine-4-yl;
s) N-methanesulfonylpiperidine-4-yl

and R^3 is selected from the group consisting of:
a) CO_2R^{20};
b) $CONR^{20}R^{23}$ and
c) CN.

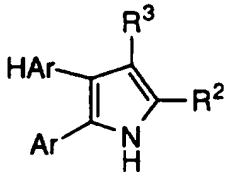
10. A compound in accordance with claim 1 represented by the formula:





11. A compound according to claim 1 falling within Table II:

TABLE II



R^2	Ar	HAr	R^3
t-butyl	Ph-4-F	3-methyl-4-pyridyl	CN
t-butyl	Ph-4-F	3-methyl-4-pyridyl	COMe
t-butyl	Ph-4-F	3-methyl-4-pyridyl	CONHMe
t-butyl	Ph-4-F	3-methyl-4-pyridyl	SO_2Et
t-butyl	Ph-4-F	3-methyl-4-pyridyl	COOEt
t-butyl	Ph-4-F	4-quinolinyl	CN
t-butyl	Ph-4-F	2-quinolinyl	CN
t-butyl	Ph-4-F	2-pyrimidinyl	CN
t-butyl	Ph-4-F	4-pyrimidinyl	CN
t-butyl	Ph-4-F	3-pyridazinyl	CN
t-butyl	Ph-4-F	2-pyrazinyl	CN
t-butyl	Ph-4-F	2-pyrimidinyl	CN
t-butyl	Ph-4-F	4-pyrimidinyl	CN
t-butyl	Ph-4-F	2-imidazo-(4,5-b)-pyridinyl	CN
t-butyl	Ph-4-F	4-(2-amino)-pyridyl	CN
t-butyl	Ph-4-F	4-(2-N-benzyl-amino)-pyridyl	CN
t-butyl	Ph-4-F	4-(2-acetylamino)-pyridyl	COMe
t-butyl	Ph-4-F	4-pyridyl	CN
t-butyl	Ph-4-F	4-pyridyl	SO_2Pr
t-butyl	Ph-4-F	4-pyridyl	CONH-iBu
t-butyl	Ph-4-F	4-pyridyl	COMe
i-butyl	Ph-4-F	4-pyridyl	CN
4-N-Me-piperidinyl	Ph-4-F	4-pyridyl	COMe
4-N-Bn-piperidinyl	Ph-4-F	4-pyridyl	COMe

4-N-Ph-piperidinyl	Ph-4-F	4-pyridyl	COMe
CH_2-4-(N-Me)-piperazinyl	Ph-4-F	4-pyridyl	CN
4-N-Me-piperidinyl	Ph-4-F	4-pyridyl	CN
4-N-Me-piperidinyl	Ph-4-Cl	4-pyridyl	CN
4-N-Me-piperidinyl	Ph	4-(2-Me)-pyridyl	CN
4-N-Me-piperidinyl	Ph	4-pyridyl	CN
t-butyl	Ph-2-OMe	4-pyridyl	CN
t-butyl	Ph-3-OMe	4-pyridyl	CN
t-butyl	Ph-4-OMe	4-pyridyl	CN
t-butyl	Ph-4-(4-N-$COCH_3$)-piperazinyl	4-pyridyl	CN
t-butyl	Ph-4-morpholinyl	4-pyridyl	CN
t-butyl	Ph-4-Cl	4-pyridyl	CN
t-butyl	Ph-3-Cl	4-pyridyl	CN
t-butyl	Ph-3,4-Cl	4-pyridyl	CN
t-butyl	Ph-3-CF_3	4-pyridyl	CN
t-butyl	Ph-4-S-Me	4-pyridyl	CN
t-butyl	Ph-4-S(O)-Me	4-pyridyl	CN
4-piperidine	Ph-4-F	4-pyridyl	CN
3-N-Me-piperidinyl	Ph-4-F	4-pyridyl	CN
CH2-morpholinyl	Ph-4-F	4-pyridyl	CN
t-butyl	Ph-4-NO_2	4-pyridyl	CN
t-butyl	Ph-4-NMe2	4-pyridyl	CN
t-butyl	Ph-2-Cl	4-pyridyl	CN
4-piperidinyl	Ph-4-F	4-pyridyl	CN
t-butyl	Ph-4-F	2-pyridyl	CN
t-butyl	Ph-4-F	2-methyl-4-pyridyl	CN

t-butyl	Ph-4-F	3-methyl-4-pyridyl	CN
cyclohexyl	Ph-4-F	4-pyridyl	CN
i-propyl	Ph-4-F	4-Pyridyl	CN
1-cyclopropyl-ethyl	Ph-4-F	4-pyridyl	CN
t-butyl	Ph-4-F	2,4-dimethylpyridyl	CN
t-butyl	Ph-4-F	2,6-dimethylpyridyl	CN.

12. A method of treating a cytokine mediated disease in a mammal in need of such treatment, which comprises administering to said mammal an effective cytokine interfering amount of a compound of claim 1.

13. The method according to claim 12 wherein the cytokine inhibited is IL-1.

14. The method according to claim 12 wherein the cytokine inhibited is TNF.

15. The method according to claim 12 wherein the cytokine inhibited is IL-8.

16. The method according to claim 12 wherein the cytokine mediated disease is septic shock, endotoxic shock, gram negative sepsis or toxic shock syndrome.

17. The method according to claim 12 wherein the cytokine mediated disease is a bone resorption disease, graft versus host reaction, atherosclerosis, arthritis, osteoarthritis, rheumatoid arthritis, gout, psoriasis or a topical inflammatory disease state.

18. The method according to claim 12 wherein the cytokine mediated disease is adult respiratory distress syndrome, asthma or chronic pulonary inflammatory disease.

19. The method according to claim 12 wherein the cytokine mediated disease is cardiac or renal reperfusion injury, thrombosis or glomerulonephritis.

20. The method according to claim 12 wherein the cytokine mediated disease is Crohn's disease, ulcerative colitis or inflammatory bowel disease.

21. The method according to claim 12 wherein the cytokine mediated disease is cachexia.

22. The method according to claim 12 wherein the cytokine mediated disease is a viral infection.

23. A method of treating inflammation mediated by a cytokine in a mammalian patient in need of such treatment, which comprises administering to said patient an amount of a compound of claim 1 which is effective to treat inflammation.

24. The method of claim 23 wherein the cytokine is IL-1, IL-6, IL-8 or TNF.

25. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17477

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 207/30, 213/32, 213/55, 239/26
US CL :514/203, 333; 544/242; 546/183, 348

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/203, 333; 544/242; 546/183, 348

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE
search terms: pyrrol?, piperidin?, pyridyl, interleukin, cytokine?, asthma, cardiac

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,442,060 A (JIKIHARA ET AL.) 15 August 1995 (15.08.95), column 55, lines 38-62.	1-11 and 25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 JANUARY 1997	11 MAR 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	JANE OSWECKI
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17477

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-11 and 25

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17477

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1.

Group I, claims 1-3, 8-11 and 25 drawn to pyrrole compounds having pyridine as the only heterocyclic substituent.

Group II, claims 1, 2, 4-6, 7, 8, 9, 11 and 25 drawn to pyrrole compounds having pyrimidine as the only heterocyclic substituent.

Group III, claims 1, 2, 11 and 25 drawn to pyrrole compounds having thiophenyl and/or furanyl as the only heterocyclic substituent.

Group IV, claims 1, 3-5, 8-11 and 25 drawn to pyrrole compounds having imidazole as the only heterocyclic substituent.

Group V, claims 1, 11 and 25 drawn to pyrrole compounds having thiazole and/or isothiazole as the only heterocyclic substituent.

Group VI, claims 1, 5, 11 and 25 drawn to pyrrole compounds having oxazole and/or isoxazole as the only heterocyclic substituent.

Group VII, claims 1, 6, 7, 11 and 25 drawn to pyrrole compounds having tetrazole as the only heterocyclic substituent.

Group VIII, claims 1, 8, 9, 11 and 25 drawn to pyrrole compounds having quinoline as the only heterocyclic substituent.

Group IX, claims 1, 3, 5, 8, 9, 11 and 25 drawn to pyrrole compounds having purine as the only heterocyclic substituent.

Group X, claims 1, 3, 11 and 25 drawn to pyrrole compounds having imidazopyridine as the only heterocyclic substituent.

Group XI, claims 1, 11 and 25 drawn to pyrrole compounds having piperazine as the only heterocyclic substituent.

Group XII, claims 1, 11 and 25 drawn to pyrrole compounds having pyridazine as the only heterocyclic substituent.

Group XIII, claims 1, 11 and 25 drawn to pyrrole compounds having pyrazine as the only heterocyclic substituent.

Group XIV, claims 1, 8, 9, 11 and 25 drawn to pyrrole compounds having imidazole[4.5-b] pyridine as the only heterocyclic substituent.

Group XV, claims 1, 11 and 25 drawn to pyrrole compounds piperidine and pyridine as the only heterocyclic substituents.

Claims 12-24 are generic to any group paid for.

Unity of invention is lacking because no single special technical feature is shared by all the groups listed, i.e. each core moiety, including (HAr), is different in structure and not known as equivalents in the art.

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

The inventions listed as Groups I-XV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: no single special technical feature which defines a contribution over the prior art is present in all of the groups, i.e., each core moiety,
including the optionally substituted HAr and Ar substituents, is different in structure and these differences are not known as equivalents in the art.

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.